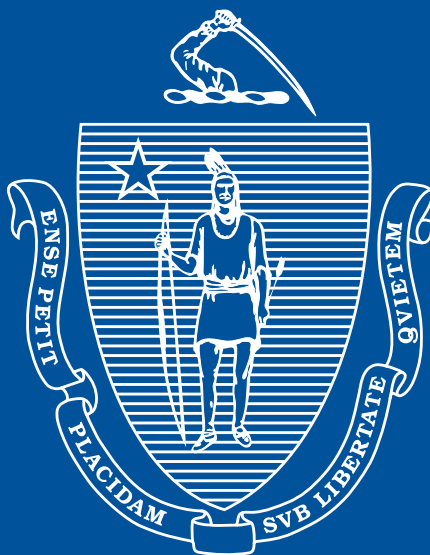


COMMONWEALTH OF MASSACHUSETTS
Executive Office of Health and Human Services

**Clinical Practice Guidelines for the Treatment of
Bipolar Disorder in Adults**



Department of Mental Health
Marylou Sudders, Commissioner

Division of Medical Assistance
Wendy Warring, Commissioner

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First Edition



**CLINICAL PRACTICE GUIDELINES
FOR THE TREATMENT OF
BIPOLAR DISORDER IN ADULTS**

Design Committee Members

Co-Chairs:

Gary Belkin, M.D., Ph.D.
Carlos Zarate, M.D.

Members:

Paul Barreira, M.D.
Nancy Blum, Psy.D.
Kenneth Duckworth, M.D.
Eden Evins, M.D.
Raymond B. Flannery, Jr., Ph.D.
M. Annette Hanson, M.D.
Deborah Moran, M.D.
Jane Musgrave, M.S., O.T.R./L.
E. Samuel Rofman, M.D.
James Slayton, M.D.
Sharon Sousa, Ed.D., R.N., C.S.

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Statement of Potential Conflict of Interest

The Massachusetts Department of Mental Health (DMH) and Division of Medical Assistance (DMA) have long held the standard that its continuing medical education endeavors be free of commercial bias.

Therefore, in accordance with guidelines set forth by the Accreditation Council of Continuing Medical Education and the American Medical Association (AMA), Design Committee Members have been asked to disclose any personal relationship that they may have to companies producing pharmaceuticals, medical equipment, prostheses, etc., that might have relevance to the content of their Design Committee efforts. Such disclosure is not intended to suggest or condone bias in any presentation, but is elicited to provide readers with information that might be of potential importance to their evaluation of this document.

Gary Belkin, M.D., Ph.D., is a Speakers Bureau member, Janssen.

Ken Duckworth, M.D., served as consultant to IVAX Corporation prior to becoming Deputy Commissioner

Eden Evins, M.D., has received Investigator Initiated Research Grants from Glaxo Wellcome and Pfizer. Dr. Evins is consultant to Abbott and Speakers Bureau member, Abbott and Janssen.

Sharon Sousa, Ed.D., R.N., C.S., is a Speakers Bureau member, Lilly and Novartis.

Carlos Zarate, M.D., has received research grant monies and has been a consultant and lecturer for Abbott, Glaxo-Wellcome, Janssen and Lilly. He has received research grant monies and has been a consultant for Pfizer and has received research grant monies from Bristol-Myers.

No other Design Committee has reported the potential for receiving something of value from a company whose product may have relevance to the content of this document.

INTRODUCTION

Mission Statement

The intent of these guidelines is to encourage the use of effective treatments, to avoid unnecessary treatments, and to outline areas where there is less than sufficient literature and, therefore, greater reliance upon the many factors balanced in the course of everyday clinical decisionmaking. These guidelines are not to be construed or to serve as a standard of care. They serve only as guidelines.

These guidelines present the published empirical studies that generally involve patients with more rigorously defined symptom profiles resulting from the restrictions of defined research protocols. These studies often indirectly guide treatment decisions shaped by the realities of clinical care such as comorbidity, complicated presentations, side effects, and individual patient histories, race, culture, and preferences.

They are therefore meant to provide an evidence-based overview of uncomplicated treatment of persons with bipolar disorders. Similarly, the treatment of acute mania within the emergency room or immediate acute management context is not addressed in these guidelines. These guidelines focus primarily on summarizing efficacy-based monotherapy symptom reduction outcome studies. For example, in this document, the Design Committee has not generally addressed the issue of how the side effects associated with these medications are balanced with the efficacy research in each individual case. Complicated and/or atypical cases of bipolar disorder will further necessitate clinical judgement, tempered by training, experience, and consultation when indicated.

These guidelines do not review all side effects, complications, interventions, or contraindications to the treatments discussed. Similarly, keeping abreast of significant changes in the research base from that reflected here is the ongoing task of the clinician.

Development of the Guidelines

The Clinical Practice Guidelines for the Treatment of Bipolar Disorder in Adults were developed by a Design Committee appointed by DMH and DMA. This committee reviewed existing treatment guidelines that included those by the American Psychiatric Association (American Psychiatric Association, 1995), the Canadian

Guidelines for the Treatment of Bipolar Disorder (Kusumakar, Yatham, et al., 1997), the Expert Consensus Guidelines (Frances et al., 1996), and the International Psychopharmacology Algorithm Project Report (Jobson & Potter, 1995). The Committee decided to base the present guidelines primarily on the Canadian Guidelines. The Committee obtained permission from the Canadian group to use, and to alter by way of additions, to their work. The Committee included the following revisions and additions:

- *The Canadian Guidelines appear in nonitalicized type. Words originally italicized in the Canadian Guidelines appear as capital letters.*
- *Committee additions and references appear in italics.*
- *To facilitate information location and retrieval, the Committee has demarcated the Canadian Guidelines into 20 sections. They are identified as Recommendations 1 through 20. The Committee then added Recommendations 21-22. These recommendations include topics and references not included in detail in the Canadian document.*
- *Appendix I is the introduction to the original Canadian guidelines.*

The Design Committee chose the Canadian Guidelines for their sound empirical footing, clarity, and general readability. This decision was not intended to set a standard of care or to imply that other treatment guidelines are inappropriate.

This document is intended to provide guidance for the treatment of individuals eighteen years or older. While many treatment issues are relevant for younger persons, the assessment and treatment of children and younger adolescents are sufficiently different to warrant separate guidelines.

The original Canadian Guidelines contained several algorithms which appeared as Figures in the original text. The Design Committee decided not to include these algorithms in this edition. For the interested reader, the points at which these figures occurred in the original published text have been noted along with the page numbers in the original text as it appeared in the Canadian Journal of Psychiatry (Kusumakar V, Yatham L.N., et al., 1997).

Many individuals were generous in reading earlier drafts of this document and the Department of Mental Health wishes to thank each reader.

General Considerations For The Treatment Of Bipolar Disorder

Bipolar disorder is a long-term illness that affects all aspects of a person's life, including but not limited to, daily living skills, physical health, vocational goals, interpersonal relationships, and other social and spiritual issues. Bipolar disorder may include periodic relapses and may require long-term support. However, recovery, defined as maximizing functioning and well-being and minimizing disability, is the desirable outcome goal. Ongoing comprehensive assessments and treatment interventions are essential, should be respectful of cultural and linguistic diversity, and should include the individual and any significant others that the individual wants to be involved.

Deciding about which treatments are pursued is a shared process between the individual seeking services and the clinician. The capacity to engage in treatment planning and decision making is presumed for all individuals seeking services. Clinicians are also obligated to make an assessment of every person's capacity to make decisions. This capacity includes the decision to discontinue treatment and needs to be performed in an initial and ongoing manner. Four generally accepted elements of this capacity are the ability to: 1.) communicate choices, 2.) understand relevant information, 3.) appreciate the situation and its consequences, and 4.) compare risks and benefits of various treatments. Based on this assessment, the clinician is bound by good clinical practices and Massachusetts law, as appropriate.

Using These Guidelines

The Canadian Guidelines advisory committee used the following classification system for its recommendations:

- A. Good support for the intervention to be considered in clinical practice
- B. Fair support for the intervention to be considered in clinical practice
- C. Poor support for the intervention to be considered in clinical practice
- D. Fair support for the intervention to be excluded from clinical practice
- E. Good support for the intervention to be excluded from clinical practice

Comments And Feedback

Any comments or feedback on these guidelines or their implementation should be sent to:

*Kenneth Duckworth, M.D.
Deputy Commissioner, Clinical and Professional Services
Department of Mental Health
25 Staniford Street
Boston, MA 02114*

Additional Committee References

American Psychiatric Association. Practice Guidelines for Treatment of Patients with Bipolar Disorder. Washington, DC: American Psychiatric Press, 1995.

Frances A, Docherty JP, Kahn DA: The expert consensus guideline series: Treatment of bipolar disorder. J Clin Psychiatry 1996; 57: Supplement 12A (whole).

Jolson KO, Potter WZ: International Psychopharmacology Algorithm Project Report. Psychopharm Bull 1995; 31:457-507.

Kusumaker V, Yatham LN, et al.: The treatment of bipolar disorder: Review of the literature, guidelines, and options. Can J Psychiatry 1997; 42 Suppl 2:69S-100S.

Sachs GS, Printz DJ, Kahn DA, Carpenter D, Docherty JP: The expert consensus guideline series: Medication treatment of bipolar disorder, 2000. Postgraduate Medicine, 2000, Special Report (whole).

Disclaimers

The Canadian Network for Mood and Anxiety Treatments Bipolar Subcommittee:

The Massachusetts Department of Mental Health and Department of Medical Assistance gratefully acknowledge the work of the Canadian Network for Mood and Anxiety Treatments (CANMAT) Bipolar Subcommittee recommendations (CANADIAN JOURNAL OF

PSYCHIATRY, 1997; 42 SUPPL 2:69S-100S). The CANMAT recommendations were developed by Dr. Vivek Kusumakar, Dr. Lakshmi N. Yatham and their subcommittee colleagues based on the evidence available at that time. Funding for the CANMAT was provided by educational grants to CANMAT from the Ontario Ministry of Health, Eli Lilly Canada, and Abbott Laboratories. The CANMAT work group had total control of the process and content of the work. Neither the Canadian government nor industry had any input into the preparation of any of these guidelines or treatment options.

The Departments of Mental Health and Medical Assistance appreciate permission to amend its guidelines in their present form. (Amendments appear in italics.) We have adopted these guidelines because we believe that they provide a clear framework with which to understand the current state of knowledge concerning the treatment of individuals with bipolar illness. We believe that they will be helpful to those who care for such individuals. However, we recognize that this is an evolving field. Treating clinicians should be mindful of their responsibility to be aware of advances in the treatment of such individuals and to determine which treatment interventions are appropriate, given the circumstances of the individual patients whom they treat.

The Canadian Network for Mood and Anxiety Treatments, its bipolar subcommittee, and their directors, officers and members, have disclaimed liability for any use of these guidelines.

Department of Mental Health/Medical Assistance Disclaimer:

These guidelines are meant to provide an overview of uncomplicated treatment of persons with bipolar disorders. By distributing these guidelines, the Departments of Mental Health and Medical Assistance do not intend to set a standard of care. Standards of medical care are determined on the basis of all clinical data available for an individual case and are subject to change as scientific knowledge and technology advance and patterns evolve. This document should be considered as providing guidelines only. Adherence to them will not ensure a successful outcome in every case. These guidelines should not be construed as including all proper methods of care directed toward the same results. There may be circumstances where legitimate and appropriate concerns

indicate the need for interventions to depart from the more common recommendations. The ultimate judgment regarding the care of a particular individual must be made by the health care provider in light of the clinical data presented by the individual and the diagnostic and treatment options available.

(Adapted from Practice Guidelines for Major Depressive Disorder in Adults. American Journal of Psychiatry. 150: 4, April 1993 Supplement P.V.)

Section One: Foundations of Management

The Foundations of Effective Management of Bipolar Disorder

Vivek Kusumakar, MBBS, FRCPC, MRCPsych¹, Lakshmi N Yatham, MBBS, FRCPC, MRCPsych², David RS Haslam, MSc, MD³, Sagar V Parikh, MD, FRCPC⁴, Raymond Matte, MD, FRCPC⁵, Verinder Sharma, MD, FRCPC⁶, Peter H Silverstone, MD, FRCPC, MRCPsych⁷, Stanley P Kutcher, MD, FRCPC⁸, Sidney Kennedy, MD, FRCPC⁹

OBJECTIVES: TO UNDERSTAND THE EPIDEMIOLOGY AND COURSE OF BIPOLAR DISORDER; TO OUTLINE THE IMPORTANCE OF ACCURATE AND RELIABLE DIAGNOSIS OF BIPOLAR DISORDER BOTH ON A CROSS-SECTIONAL AND LONGITUDINAL BASIS; AND TO EMPHASIZE THE VALUE OF A COLLABORATIVE THERAPEUTIC RELATIONSHIP, PSYCHOEDUCATION, AND PSYCHOTHERAPY.

METHODS: A BRIEF REVIEW OF RELEVANT LITERATURE TO DEAL WITH THE ISSUES OF DIAGNOSIS AND LAYING THE FOUNDATIONS FOR EFFECTIVE TREATMENT.

RESULTS: BIPOLAR DISORDER MAY WELL BE A HETEROGENEOUS GROUP OF CONDITIONS WITH VARYING FORMS OF BIPHASIC MOOD DYSREGULATION AND A CHANGING COURSE ACROSS A LIFETIME. A COLLABORATIVE THERAPEUTIC RELATIONSHIP, PSYCHOEDUCATION, AND PSYCHOTHERAPY CAN BE THE BASIS FOR EFFECTIVE MANAGEMENT.

CONCLUSIONS: AS THE CONCEPT OF BIPOLAR DISORDER HAS BROADENED, THE CONDITION IS BEING IDENTIFIED WITH INCREASING FREQUENCY IN MANY CLINICAL SETTINGS. IT IS A RELAPSING AND RECURRING CONDITION. IT IS NOW RECOGNIZED THAT IN ADDITION TO RATIONAL PHARMACOTHERAPY, THERE IS A NEED TO ENCOURAGE A HIGH LEVEL OF TREATMENT ADHERENCE WHILE PROVIDING A HOLISTIC PACKAGE OF INTERVENTIONS.

(Can J Psychiatry 1997;42 Suppl 2:69S-73S)

KEY WORDS: EPIDEMIOLOGY, COURSE, DIAGNOSIS, ASSESSMENT, PSYCHOEDUCATION, PSYCHOTHERAPY

As the concept of bipolar disorder has broadened, the condition is being identified with increasing frequency in many clinical settings. Although many available treatments are effective in both acute states and prophylaxis, the efficacy of interventions is far from satisfactory, with patients with bipolar disorder experiencing significant relapses and recurrences (1-4). The guidelines we propose focus on biological and psychotherapeutic treatments used for patients with bipolar type I disorder as defined previously in DSM-III-R and currently in DSM-IV. These treatment options and guidelines may be relevant for some other conditions with significant biphasic mood dysregulation, including bipolar type II disorder and schizoaffective illness.

The authors recognize that the recommendations provided are not comprehensive. They are intended to build upon rather than replace good clinical skill and sound clinical experience. The suggested approach is based upon a synthesis of the best external evidence and expert opinion. This should be integrated with individual clinical expertise, as well as patients' needs and choices, to provide optimal care.

The evidence in support of these guideline proposals was derived from the results of studies which, in many instances, have limited generalizability. The characteristics of a general patient population may differ significantly from those of patients included in research studies and clinical trials. Physicians and other clinicians should identify how much their patients are like those in the studies that have been cited and recognize that individual patient needs are variable and require skillful judgement not only about treatment choices but also about the timing of interventions. Further, because comorbid disorders are not uncommon (5) but are more often than not excluded from clinical trials, the treating clinician should feel free to go beyond the scope of these recommendations whenever required.

Every effort should be made to identify and treat biphasic mood dysregulation precipitated, caused, or exacerbated by alcohol, substance abuse, or a variety of general medical as well as neurological conditions (6-10).

Epidemiology, Clinical Presentations, and Course

Weissman has reported that bipolar type I disorder affects between 0.4% and 1.6% of the population, whereas bipolar II disorder may be relatively more common than previously recognized

(11). There are no gender or racial differences in the prevalence of bipolar I disorder, although bipolar II disorder is reportedly more common in women.

The average age of onset for bipolar disorder is in the early to mid-20s. The concept of the mean age of onset, however, does not highlight the fact that the largest peak age of onset of first symptoms is likely between the age of 15 and 19 years (12-14). The condition is commonly undetected, untreated, or undertreated. Often there is a 3- to 10-year time lag between the age of onset of the illness and the age at which the first treatment or hospitalization occurs. Further, bipolar types I and II are commonly preceded by chaotic fluctuation of mood and behaviour for months to years prior to the condition being recognized as meeting major mood disorder criteria (14,15).

Although the initial episode of mood dysregulation is commonly depression in females and mania in males, any patient may experience several episodes of depression before the onset of a manic episode. Early-onset bipolar disorder is more commonly associated with depression as the first mood disorder episode (14-17). *Therefore, it is important to attempt to ascertain whether there is a family history of bipolar disorder in all patients presenting with what may appear to be new onset unipolar depressive illness as this illness runs in families.* In patients with an onset of bipolar disorder after the age of 60 (18,19), the disorder is more likely to be associated with identifiable general medical and neurological conditions, higher morbidity and mortality rates, and the absence of significant association with a positive family history for the illness.

Diagnostic assessment should include not only determination about the presence of depressive and/or hypomanic and manic features but also whether the patient has a mixed or rapid-cycling state (20); psychotic features; suicidality; risk of significant harm to others; alcohol and/or other substance abuse; social, financial, and sexual risk-taking behaviours; a childbearing status or plans; and the presence of cognitive or functional impairment. It is also important to chart the course and chronology of subthreshold symptoms and mood disorder episodes (21). *Please see appendix for sample monthly mood chart. The use of a monthly mood chart may be helpful. The patient fills out daily as a tool that may increase patients' understanding of their mood cycles, improve their ability to note warning signs of impending relapse and improve treatment adherence.* All of this diagnostic information can be vital in selecting the most appropriate specific treatment for a given patient at a given time in the course of the illness.

Bipolar disorder is an episodic, long-term illness. Inadequately treated patients often have more than 10 episodes of biphasic mood disorder during their lifetime, with interepisode intervals narrowing

as age advances (22). There is an increased risk of suicide, reported to be between 17% and 19% (23,24), and there is significant disruption in psychosocial functioning, with severe impairment of quality of life for the sufferer and his or her family (25). Bipolar disorder is the most likely of Axis I disorders to occur with alcohol or substance abuse (5). Recent evidence suggests that bipolar patients who abuse drugs or alcohol have an earlier onset and more severe course of illness compared with those who do not (26). *There is some evidence that clinicians in the United States misdiagnose bipolar I disorder as schizophrenia, when treating African Americans and younger individuals* (Castillo, 1997; Mukherjee et al., 1983).

There is evidence to support the use of pharmacotherapy in the acute and prophylactic phases of bipolar disorder. Pharmacotherapy may substantially reduce the risk of suicide in these patients (27,28). In addition to pharmacotherapy, there is increasing interest in the role of psychotherapy in bipolar disorder and its relationship to improving treatment adherence, which can itself affect prognosis (29-31).

Recommendation 1: Careful Assessment and Reassessment

Assessment and Reassessment

Careful assessment, monitoring, and rapid reassessment as necessary are essential in making an accurate diagnosis of bipolar disorder. This approach is also required to understand the cross-sectional and longitudinal characteristics of a condition that can fluctuate, often abruptly, in its presentation. The use of a simple mood diary and course of illness chart can be valuable diagnostically and provide a longitudinal view of the patient's symptoms and course. Readers should be aware that biphasic mood dysregulation, whether it meets the full threshold criteria for a bipolar disorder as per DSM-IV or not, can coexist with a variety of other Axes I, II, or III conditions and may benefit from mood stabilizer treatment in conjunction with other treatments. Bipolar disorder may also be underdiagnosed. Clinicians should monitor their own tendencies to underdiagnose or overdiagnose biphasic mood dysregulation. Thus a thorough and valid multiaxial assessment and diagnostic formulation must form the cornerstone of practice before one can examine any treatment options and guidelines. Of course, there will always be patients who do not fit neatly into any category or whose primary diagnosis is unclear. This is commonly the case with patients who have biphasic mood dysregulation with comorbid alcohol or substance abuse. Such patients may benefit from individualized treatment algorithms that will allow for systematic testing or diag-

nostic or treatment hypotheses.

Diagnostic assessment and reassessment are particularly important for patients for whom treatment has been partially effective or for whom relapse of symptoms has occurred. Below are specific recommendations that may be useful regarding assessment in specific circumstances such as no improvement in symptoms after initial treatment, partial improvement in symptoms, and relapse of acute mood symptoms while on stable treatment regimen.

- 1. Reassess diagnosis with careful attention to symptom profile, atypical symptoms, family history, co-morbid illness such as untreated psychosis, substance abuse or medical co-morbidity.*
- 2. Assess treatment alliance and medication compliance.*
- 3. Assess for presence of acute life stressors and psychosocial factors that may affect mood or treatment compliance.*
- 4. Evaluate medication dosage and duration of treatment for adequacy and consider measuring serum concentrations of medications.*
- 5. Consider obtaining information regarding which medications have been effective for affected family members.*
- 6. Assess confounding factors such as loss of medication response and potential effects of medications prescribed by other treaters.*
- 7. Refer for diagnostic consultation when questions regarding diagnosis persist.*
- 8. Integrate the understanding of culture of the patients into clinical practices.*

A positive family history of bipolar disorder *may* increase the probability of a patient *who presents initially* with a major depressive episode developing biphasic mood disorder (32). In children, adolescents, or young adults, the presence of psychotic depression or recurrent bouts of atypical depression or depression with obsessive-compulsive features should raise a strong suspicion of the future advent of bipolar disorder (13). This progression to bipolar illness is of particular concern in the presence of a family history of the disorder. A careful history from the patient, key informants, and, if necessary, a longitudinal monitoring of mood using a mood diary, can help establish if the patient suffers from or has suffered from episodes of mania or hypomania. Even if a diagnosis of bipolar disorder cannot be confidently established, the risk factors for the future development of bipolar disorder described above should influence the clinician to plan or use interventions that have a lower risk of switching the patient into manic, rapid-cycling, or mixed states.

Careful monitoring and rapid reassessment of a patient's clinical

presentation (that is, severity of mood disorder or presence of rapid-cycling, mixed state, or psychotic features) not only influence immediate and possibly long-term prognosis but also may guide the clinician toward the use of specific treatments for particular clinical presentations (33-37).

Recommendation 2: Establishing an Effective Treatment Alliance

Establishing Treatment Alliance and the Role of Psychoeducation and Psychotherapy

Whereas rational pharmacotherapy is effective and often central in the management of bipolar disorder, establishing a sound therapeutic alliance with a patient with bipolar disorder is the foundation of effective treatment. The acute bipolar, subsyndromal mood fluctuation, and prolonged remission phases are often found to be the most taxing on the therapeutic relationship and on treatment adherence. An understanding of the patient, his or her family, and his or her key friends' attitudes, understanding, and responses to psychiatric illness can help the clinical team develop particular strategies for support, monitoring, and therapeutic interventions. *In addition, an understanding of their cultural and socioeconomic identity, explanation of mental illness, expression of symptoms, and help seeking behaviour is critical to provide the appropriate assessment and treatment. Such understanding and integration into clinical assessment and interventions are crucial in enhancing treatment adherence and positive outcome (U.S. Department of Health and Human Services, 1999).*

While instilling hope, the clinician and team also need to help the patient, family, and friends understand the recurrent and fluctuating nature of the illness, the associated morbidity and mortality, and the opportunities for the implementation of effective treatment. The effective and empathic management of feelings of denial, guilt, self-blame, and hostility in the setting of appropriate psychoeducation can significantly improve the potential for a healthy therapeutic alliance and development of a collaborative, individualized treatment plan, thus improving the potential for treatment adherence. Having optimum treatment adherence can significantly reduce the risk of relapse and its associated problems, including increased morbidity and mortality (31,32,38,39).

One must not underestimate the possibility of nonadherence to a treatment regimen by patients, families, and treatment systems. Patients often use denial or minimalization in understanding their condition and its effects on themselves and those around them. A significant number of patients are also very reluctant to give up the

pleasurable aspects of increased drive and energy, inflated self-confidence, and the feeling of a “high” that goes with hypomania and mania. If they perceive treatment as reducing their productivity and creativity, or perceive hypomania and mania as an effective counter to miserable and hopeless depression, compliance with treatment is often diminished (39-42). Adverse effects, plans for pregnancy, teratogenic risks, and negative views about medications in the patient, family, friends, and health care professionals also affect treatment adherence (43).

Very early in the management of the patient with bipolar disorder, there is a need to establish healthy social and biological rhythms. It is well established that sleep deprivation can provoke hypomania and mania and that substance abuse can induce or maintain a mood disorder. Having healthy patterns of sleep, nutrition, social interaction, physical activity, and involvement in tasks, school, or a job that is socially, emotionally, and/or financially rewarding can all be significantly beneficial in the treatment of mood disorder (31,44-46).

Although bipolar disorder is not a curable condition, it can be effectively managed with a combination of psychoeducational, pharmacotherapeutic, psychotherapeutic, and social interventions. *Additional efforts should be made to integrate culturally appropriate assessment and therapeutic interventions, rehabilitation and psychoeducation in working with culturally diverse population.* Hence the prevention of recurrences and relapses deserves great attention. These recurrences or relapses can have a cumulative deteriorative effect on functioning and treatment response. Early diagnosis and optimal treatment, therefore, can significantly improve the chances of recovery, remission, improved functioning, and a better quality of life (3).

Recommendation 3: Psychoeducation and Psychotherapy for Patients and Families

It is very useful to assist the patient and family to identify a supportive network of people who will, in an effective yet nonstigmatizing manner, help the patient to seek early intervention in a newly developing episode of mood disorder. Patients benefit significantly from making plans that instill hope while being directed toward realistic, tangible, and attainable goals. Patients often require active assistance to maintain and not jeopardize key relationships, employment, or financial status during the prodrome or actual acute major mood disorder episode. Concerns that patients may have about the risk of bipolar disorder in siblings or progeny should be taken seriously and addressed through genetic counseling or

timely assessments of at-risk family members who may demonstrate subthreshold symptoms of mood disorder (32).

Helping the patient and his or her support network to identify the early warning signs of impending mood disorder (for example, sleep disturbance, changing patterns of alcohol use, interpersonal relationship problems, and dysfunctional academic or work behaviour) allows for timely changes in the intensity or type of treatment intervention. Such a plan of action can improve the patient's sense of hope, promote a feeling of mastery, and foster a collaborative approach to management. A graphic and concrete view of paradigms of chronic physical illness and its treatment, for example, diabetes mellitus, can help patients and families work through the issues of a long-term disorder and the necessity for extended treatment and monitoring.

Clinical Implications

- Bipolar illness is a common clinical problem.
- Bipolar disorder can be effectively treated with a combination of medications and psychosocial interventions.
- Noncompliance with medications is common in patients with bipolar disorder.

Limitation

- Many factors have to be taken into account in devising a treatment plan for bipolar disorder.

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¹Associate Professor and Head, Division of Child and Adolescent Psychiatry; Director, Mood Disorders Group, Department of Psychiatry, Dalhousie University, Halifax, Nova Scotia.

²Assistant Professor and Director, Mood Disorders Clinical Research Unit, Department of Psychiatry, University of British Columbia, Vancouver, British Columbia.

³Resident, Department of Psychiatry, Dalhousie University, Halifax, Nova Scotia.

⁴Assistant Professor, Department of Psychiatry, University of

Toronto; Head, Bipolar Clinic, Clarke Institute of Psychiatry, Toronto, Ontario.

⁵Associate Professor (Clinical) and Head, Outpatient Services and Mood Disorders Clinic, Department of Psychiatry, University of Sherbrooke, Sherbrooke, Quebec.

⁶Assistant Professor and Director, Mood Disorders Unit, Department of Psychiatry, University of Western Ontario, London, Ontario.

⁷Associate Professor, Department of Psychiatry, University of Alberta, Edmonton, Alberta.

⁸Professor and Head, Department of Psychiatry, Dalhousie University, Halifax, Nova Scotia.

⁹Professor, Department of Psychiatry, University of Toronto; Head, Mood and Anxiety Disorders Division, Clarke Institute of Psychiatry, Toronto, Ontario.

ADDRESS FOR CORRESPONDENCE: Dr. V Kusumakar, Department of Psychiatry, Dalhousie University, IWK-Grace Health Centre, 5850 University Avenue, Halifax, NS B3J 3G9
email: vkusumakar@usa.net

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Section Two: Psychosocial Interventions

Psychosocial Interventions as an Adjunct to Pharmacotherapy in Bipolar Disorder

Sagar V Parikh, MD, FRCPC¹, Vivek Kusumakar, MBBS, FRCPC, MRCPsych², David RS Haslam, MSc, MD³, Raymond Matte, MD, FRCPC⁴, Verinder Sharma, MD, FRCPC⁵, Lakshmi N Yatham, MBBS, FRCPC, MRCPsych⁶

OBJECTIVE: TO SUMMARIZE THE EVIDENCE AND MAKE TREATMENT RECOMMENDATIONS REGARDING THE USE OF PSYCHOSOCIAL INTERVENTIONS AS AN ADJUNCT TO PHARMACOTHERAPY FOR BIPOLAR DISORDER.

METHODS: WE REVIEWED PUBLISHED OUTCOME STUDIES SINCE 1975 IDENTIFIED IN MEDLINE AND PSYCHLIT SEARCHES.

RESULTS: AVAILABLE STUDIES ARE INITIAL AND OF HIGHLY VARIABLE METHODOLOGICAL RIGOUR. EVIDENCE IS MOST ROBUST FOR THE EFFICACY OF PSYCHOEDUCATION AND FAMILY THERAPY, AND THESE RECEIVED THE HIGHEST LEVEL OF RECOMMENDATION AS INTERVENTIONS. GROUP THERAPY, COGNITIVE-BEHAVIOURAL THERAPY, AND BEHAVIOURAL FAMILY MANAGEMENT THERAPY ARE SUPPORTED BY WEAKER EVIDENCE AND RECEIVED A LOWER-LEVEL TREATMENT RECOMMENDATION. AVAILABILITY OF ONLY A SINGLE INTERPERSONAL AND SOCIAL RHYTHMS THERAPY TRIAL LIMITED THE CONFIDENCE OF THE RECOMMENDATION FOR THIS INTERVENTION.

CONCLUSIONS: CONTROLLED TRIALS ARE NEEDED TO REPLICATE EARLY OUTCOME STUDIES AND GUIDE TREATMENT RECOMMENDATIONS. ACCUMULATED EVIDENCE OF FAVOURABLE PSYCHOSOCIAL INTERVENTION OUTCOMES SUPPORTS, WITH VARIABLE CONFIDENCE, THEIR USE AS ADJUNCTS TO PHARMACOTHERAPY IN THE TREATMENT OF BIPOLAR DISORDER.

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KEY WORDS: BIPOLAR, PSYCHOSOCIAL, PHARMACO-

THERAPY, PSYCHOEDUCATION, FAMILY THERAPY, GROUP THERAPY, COGNITIVE THERAPY, BEHAVIOURAL FAMILY MANAGEMENT THERAPY, INTERPERSONAL THERAPY, SOCIAL RHYTHM THERAPY

Bipolar disorder is often associated with severe social and occupational deficits that persist after the acute phase and during maintenance on pharmacotherapy (1-3). The majority of discharged bipolar patients experience functional impairment after discharge from hospital (4). These issues reflect the impact of a number of problems relating to the disorder: acceptance of the illness by the patient and family, adherence to medication and other management, alcohol and substance abuse, *suicide, possible victimizations*, and social risk factors. Financial and employment difficulties (5), self-esteem injury, divorce (6), and relationship dysfunction (5) are all losses the bipolar patient may have to face. Anticipated lack of fulfilment in future relationships or educational and occupational plans may also contribute to a sense of loss. Because bipolar disorder is a chronic illness with recurrences and relapses, denial, anger, ambivalence, and anxiety may develop as the patient and family adjust to the diagnosis (7). Denying or minimizing the vulnerability of relapse is a coping mechanism often adopted by those with the illness and their caregivers. Prodromal mood instability preceding the development of the disorder frequently predisposes the patient and family to conflict (8).

Recommendation 4: Therapeutic Alliance and Psychoeducation

Therapeutic Alliance

All psychosocial and medical interventions need to be employed with sensitivity to the importance of the therapeutic relationship between the individual and the provider. A supportive therapeutic relationship should be established in order for the individual to trust the clinician and the team, and thus collaborate with treatment. This relationship will also inform the clinician of early symptom relapse. Part of an essential ingredient of this alliance is an atmosphere in which the individual may feel free to discuss various aspects of his or her illness, including satisfaction or dissatisfaction with medications. The clinician and/or team should create an atmosphere in which the individual can feel free to discuss what he/

she experiences as negative in the treatment process so that continued participation in meaningful and effective treatment is enhanced. Periodic reassessment of the treatment plan, including a psychosocial history, in collaboration with the individual, to make modifications in accord with the individual's preferences and needs should be practiced. The clinician and/or team should work closely with the individual's family when permission is given. Decisions about which treatments are pursued is a shared process between the individual seeking services and the clinician. For the clinician and/or team working with individuals who are culturally diverse, regular consultation with a competent bilingual and bicultural clinician or cultural consultant should be strongly considered when the clinician and/or team are not familiar with the individuals' culture. For individuals who are limited or non-English speakers, the availability of a competent interpreter for the clinician and/or team at all times is critical.

Maladaptive coping frequently involves ignoring recommended pharmacotherapy regimens, which results in illness exacerbation (9). In recent-onset manic patients, partial compliance rates with lithium have been reported to be as high as 70% (3), and noncompliance rates often reach 60% on this medication (10-12). Almost all compliant patients seriously consider discontinuing lithium at some stage, and if they do, they discontinue it abruptly (13). Patients receiving carbamazepine may have higher rates of adherence (14). The prediction of medication noncompliance is complicated by the contribution of numerous factors, including the nature of the patient-physician relationship (15), the patient's understanding of the illness, previous history of poor medication adherence (7), and patient dislike of having "mood controlled" (10). Abrupt discontinuation of medication carries with it a high risk of relapse (17).

The frequency and the timing of illness episodes are probably affected by social environment stressors (18). Prior to illness recurrence, bipolar patients seem to experience more life events than controls without mental illness (19,20), *perhaps including developmental stressors such as early parental loss* (Agid, 1999), and in a prospective study, the relative risk of recurrence was markedly elevated in those with high life stress scores (21, Hammen & Gitlin, 1997). Several prospective studies have reported a positive correlation between high expressed emotion as a measure of family affective tone and poor outcome among bipolar patients (3,22).

Various psychotherapeutic approaches have been used with bipolar patients with putative mechanisms of change hypothesized to involve closer monitoring of affective symptomatology, earlier environmental modification following life events, enhanced compliance with pharmacotherapy, enhanced social support, improved

familial adjustment, regulation of daily routines, and enhancement of coping strategies (23). The major psychotherapeutic modalities that may be helpful for some patients are psychoeducation, group therapy, cognitive-behavioural therapy, family therapy, and the 2 newer therapies of interpersonal and social rhythm therapy, and behavioural family management for bipolar disorder. The evidence supporting these interventions suffers from considerable methodological shortcomings. The recommendation to include a psychosocial dimension of care in selected patients is based on a strong clinical consensus that there is at least preliminary support for psychosocial interventions as an adjunct to pharmacotherapy. This situation may soon be improved as several methodologically rigorous trials using manualized psychotherapies as an augmentation to medication maintenance are now in progress (24). Although the recommended psychosocial modalities will be discussed separately, clinical practice often involves a synthesis of approaches adapted to the patient's needs and preferences, as well as the therapist's resources.

Psychoeducation

Psychoeducation has been an important component of many of the group and family interventions reported below, with evidence suggesting that this psychoeducational component was important in facilitating compliance with treatment and favourable clinical outcome. Several controlled studies used the psychoeducational approach exclusively and reported enhanced compliance with lithium. A 6-session psychoeducation intervention, designed from a cognitive therapy perspective, improved lithium compliance and clinical outcome in a randomized controlled trial (25). In that study, patients receiving the intervention had a lithium noncompliance of 21% and significantly fewer hospital admissions than the control group, which received "treatment as usual" and had a lithium noncompliance rate of 57%. In another study, bipolar patients randomized to formal educational lectures on video tape and a written transcript significantly enhanced both their attitude toward and compliance with lithium as compared with the control group (26,27).

Psychoeducation may also be effective in improving patients' partners' knowledge about the illness, medication, and social support strategies for at least 6 to 18 months (28,29), but the effect of these interventions on major mood disorder relapse and retention of educational benefit is not known.

Psychoeducation should include but not be limited to the following topics as appropriate:

1. *Recognition and acceptance of illness*
2. *Identifying triggers to relapse and early signs of trouble*
3. *Standardizing daily routines*
4. *Dealing with friends and family and minimizing stressors*
5. *Learning how to cope with mood changes*
6. *Medication education*
7. *Potential risks of substance use*
8. *Information about self-help groups*
9. *Family Planning*
10. *Risk of sexually transmitted diseases*
11. *Information regarding resources and referrals to support services such as, Day Treatment, Social Day Programs, Supported Education and Employment (SEE), the American Psychiatric Association (www.psych.org), the American Psychological Association (www.APA.org), Career Centers (www.looksmart.com), the Knowledge Exchange Network (www.mentalhealth.org), the Manic Depressive Association (www.namda.org), Mass Rehabilitation Commission (MRC)(www.state.ma.us/mrc.htm), the National Alliance for the Mentally Ill (www.nami.org), and the National Institute for Mental Health (www.mentalhealth.org), [These references should not be considered an endorsement of the sources cited. The Committee has not reviewed the content of the information distributed by these organizations or that which is posted on their websites. There are many other sources of information and referrals which are available to individuals, their caregivers, and clinicians.]*
12. *Efforts should be made to make psychoeducation understandable, given the individual's language, culture, and reading level. Overall, the quality of evidence for psychoeducation is "1," that is, there is at least one randomized controlled trial, and the working group classification of recommendation was "A," that is, good support for the intervention to be considered in clinical practice.*

Recommendation 5: Family Therapy

Family Therapy

Early reports of eclectic-based family therapy in bipolar patients without systematic follow-up concluded that this intervention could enhance lithium compliance, reduce relapse, and improve family communication (30). Subsequently, several other more systematic family therapy studies have reported improvement in global outcome. A randomized controlled trial of 6 inpatient family intervention sessions in 169 inpatients assessed global function outcome 18

months after discharge. Of the 21 bipolar patients (14 female) in the treatment group, the female patients demonstrated immediate and long-term improvement in social, family, leisure, and occupational performance, as well as family attitude toward treatment, compared with the female controls and male bipolar patients, who demonstrated either no benefit or negative effect (31,32). Interpretation of this study is limited by unreported rates of illness relapse or rehospitalization and uncertainty about control of the medication regimen.

Overall, the quality of evidence for family therapy is “1,” that is, at least one randomized control trial, and the working group classification of recommendation was “B,” that is, fair support for the intervention to be considered in clinical practice.

Due to scheduling and other constraints, family therapy may be difficult to fully utilize. However, family members can and should be integral partners in the rehabilitation process through regular involvement and contact, as confidentiality allows. There is a wide spectrum and level of involvement that the family may have in the treatment plan so that treatment plans can reflect the uniqueness of each family system. The family often has more contact and a longer history with the individual, which can often have a positive effect on treatment outcomes.

Recommendation 6: Group Therapy

Group Therapy

Several open, uncontrolled trials provide the most robust assessment of group therapy (plus lithium) in the treatment of bipolar patients. The overall frequency and length of hospitalization per year diminished (16.8 to 3.6 weeks of hospitalization per year), while rates of regular employment and lithium compliance significantly improved over 2 years among 13 lithium-responsive bipolar patients involved in interpersonal group therapy (33). A follow-up report on this trial noted a generally higher rate of lithium compliance in the group therapy patients. Delineating the psychotherapy-specific effects from the nonspecific effects of close follow-up, however, is not possible (34). Outpatient group therapy in bipolar patients (12 women, 10 men) focusing on interpersonal relationships has been reported to reduce hospital admissions over a 4-year period (35). The significance of these results is uncertain given a dropout rate of greater than 50%. The persistence of reduced hospitalization rates and improved psychosocial and economic functioning was perceived to have been a benefit of group therapy and has extended beyond a decade of the intervention (36). Group psychotherapy in

combination with psychoeducation and case management may also be an effective approach in the male geriatric outpatient population (37).

Overall, the quality of evidence for group therapy was “2.3,” that is, very significant results from uncontrolled trials from more than one centre comparing results with and without interventions, and the working group classification of recommendation was “C,” that is, poor support for the intervention to be considered in clinical practice.

Recommendation 7: Cognitive Therapy

Cognitive Therapy

The cognitive-behavioural literature in the treatment of bipolar disorder is sparse. Cognitive therapy principles were employed in the psychoeducation intervention described earlier. Open reports have suggested a role for cognitive therapy in bipolar depression (23; Zaretsky 1997, unpublished observations). A cognitive-behavioural therapy and psychoeducation-oriented treatment manual was recently designed for the purpose of improving medication compliance and promoting patient awareness of maladaptive information processing in an attempt to prevent illness relapse (38).

Overall, the quality of evidence for cognitive therapy rated a “3,” that is, opinions of respected clinical authorities based on clinical experience, descriptive studies, or reports of expert committees, and the working group classification of recommendation was “B,” that is, fair support for the intervention to be considered in clinical practice. This recommendation was made despite the limited amount of evidence in view of the strong evidence for its efficacy in unipolar depression and the likelihood that cognitive therapy does not pose significant risks of side effects or a switch into mania.

Recommendation 8: Behavioural Family Management Therapy

Behavioural Family Management Therapy

Adapted from a therapeutic approach used in schizophrenia treatment, this social skill- and education-based family therapy consists of a functional assessment of the family unit, psychoeducation, and training in communication and problem-solving skills (39,40). Twenty-one sessions over 9 months, with additional crisis intervention as required, comprises the treatment. A small (N = 9) uncontrolled trial of this therapy conducted in the

setting of close medication monitoring revealed an 11% rate of mood disorder recurrence during a 9-month posthospital follow-up (39). Randomized controlled behavioural family management clinical trials are currently in progress (40).

Overall, the quality of evidence for behavioural family management therapy merits a “3,” that is, opinions of respected clinical authorities based on clinical experience, descriptive studies, or reports of expert committees, and the working group classification of recommendation was “C,” that is, poor support for the intervention to be considered in clinical practice.

Recommendation 9: Rehabilitation Services and Interpersonal and Social Rhythm Therapy

Rehabilitation Services

Persons with bipolar disorder who have any of the following characteristics should be offered Rehabilitation Services which may include but are not limited to Occupational Therapy and Vocational Rehabilitation. Rehabilitation Services are indicated if the person demonstrated functional deficits that significantly interfere with participation in daily life responsibilities, roles, and interests. Such areas include: 1) Activities Of Daily Living: grooming, dressing, feeding, medication routine, health maintenance, socialization, functional communication, functional mobility, emergency response, 2) Work and Productive Activities: home management, care of others, educational opportunities, vocational activities, and 3) Leisure Exploration And Leisure Performance: which include the ability to experience and identify new and personally fulfilling leisure interests and the ability to engage and increase skill levels in activities of past leisure pursuits.

Occupational Therapy Services provide functional capacity evaluations, treatment, and environmental adaptations to maximize an individual's physical and cognitive abilities. Such services can be useful when determining an individual's readiness to resume life roles and responsibilities (school, work, parenting, driving, etc.) after manic or depressive episodes. Occupational Therapy assists individuals in establishing healthy daily routines and balancing individuals' roles and responsibilities (American Occupational Therapy Association, 2000).

Vocational Rehabilitation Services provides work skill evaluations and training in work skill development. These interventions enhance the individual opportunity to increase functional vocational skills and improve the work behaviours needed to find, obtain, and maintain gainful employment.

Interpersonal and Social Rhythm Therapy

This therapeutic model attempts to unify the social and interpersonal models of affective disorder and the social rhythm stability hypothesis (24,41-43). This hypothesis proposes that mood regulation is in part a function of the regularity of daily activity and social stimulation patterns insofar as these patterns affect biologically based circadian rhythms. According to this model, derived primarily from observations in unipolar depressed patients, mood-disordered patients are particularly susceptible to social and circadian rhythm change (18,42). The goal of interpersonal and social rhythm therapy is to standardize a patient's daily rhythms and resolve key interpersonal problems that destabilize the mood state and/or daily rhythm (24,43). Preliminary evidence from a randomized clinical trial suggests that this therapy with medication is associated with improved regularity of daily rhythms over 52 weeks as compared with control group patients from the same outpatient medication clinic (44). The effect of this intervention on medication compliance, global functioning, and illness course, however, is uncertain at this stage.

Overall, the quality of evidence is "1," that is, there is at least one randomized controlled trial of this intervention, but the working group classification of recommendation was only "C," in other words, there was poor support for the intervention to be considered in clinical practice in view of the reliance on a single study without sufficient replication and without extensive published data on the clinical outcomes. The working group recognized, however, that like cognitive therapy, interpersonal and social rhythm therapy presents low risks to patients who are also on other adequate treatment and that the normalizing of social and biological rhythms can be beneficial.

Quality of Psychosocial Evidence

Few studies employed outcome measures that had been demonstrated to be both valid and sufficiently reproducible. Only psychoeducation, cognitive therapy, and brief inpatient family therapy interventions with follow-up during the continuation phase of the illness are supported by some trials, one of which was a single published trial in which bipolar patients were randomized to either the intervention of interest or control treatment (25,27,32). Small sample sizes often increase the risk of a type II error. To date there are no published randomized controlled trials examining the efficacy of interpersonal, behavioural, cognitive, marital and family, group, or social rhythm therapies in bipolar disorder maintenance treatment.

Although research on psychosocial interventions in bipolar disorder is limited and subject to methodological flaws, a recent review article of 32 peer-reviewed studies (Huxley, Parikh, & Baldessarini, 2000) reported on 14 groups, 13 couples or family, and 5 individual therapy interventions in conjunction with standard pharmacotherapy. The sample included a total of 1052 patients. These studies utilized psychoeducational, interpersonal or cognitive-behavioural approaches and reported consistent beneficial effects, which included reduced morbidity, reduced hospitalizations, improved social functioning, and/or improved vocational functioning. While additional research is needed, the results to date strongly support the use of psychosocial approaches with standard psychopharmacology in treating bipolar patients.

Clinical Recommendations

Available research and clinical experience provide strong evidence to support the use of psychoeducation, regardless of the phase of the disorder, but particularly in the first few episodes. The best format for psychoeducation—individual, group, or family-based intervention—remains unclear; each type has some demonstrated efficacy. Maintaining a treatment alliance must remain as a principal objective throughout all phases, relying on supportive therapy principles when the patient is more acutely ill. During the manic phase, no formal psychotherapies have been demonstrated to be useful; instead, psychotherapeutic techniques such as alliance building, limit setting, supportive measures, reduction of stimuli, and behavioural techniques may be needed. During the depressed phase, cognitive-behavioural therapy should be considered for selected patients, particularly those with mild bipolar depression. Some evidence exists to support the use of interpersonal and social rhythm therapy interventions during the continuation and maintenance phases of bipolar treatment. Substantial evidence suggests a role for family therapy intervention in selected cases to reduce stigmatization and negative expressed emotion, which may provoke relapse *and to provide education to improve an individual's ability to recognize the signs and symptoms of relapse*. Patient utilization of support and advocacy groups, for example, the Canadian Mental Health Association and the National Depression and Manic Depression Association, may also be beneficial.

Clinical Implications

- Maintaining a treatment alliance must remain a principal objective throughout all phases, relying on supportive therapy principles when the patient is more acutely ill.
- During the manic phase, no formal psychotherapies have been demonstrated to be useful; instead, psychotherapeutic techniques such as alliance building, limit setting, supportive measures, reduction of stimuli, and behavioural techniques are potential strategies.
- During the depressed phase, cognitive-behavioural therapy or interpersonal and social rhythms therapy should be considered for selected patients.
- Substantial evidence suggests a role for family therapy intervention in selected cases to reduce stigmatization and negative expressed emotion, which may provoke relapse.
- Psychoeducation can be a valuable tool in promoting therapeutic alliance and a collaborative approach to effective treatment.

Limitations

- Review of literature is narrative and data are not quantitatively analyzed.
- Evidence available is initial, is of variable methodological quality.

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¹Assistant Professor, Department of Psychiatry, University of Toronto; Head, Bipolar Clinic, Clarke Institute of Psychiatry, Toronto, Ontario.

²Associate Professor and Head, Division of Child and Adolescent Psychiatry; Director, Mood Disorders Group, Department of Psychiatry, Dalhousie University, Halifax, Nova Scotia.

³Resident, Department of Psychiatry, Dalhousie University, Halifax, Nova Scotia.

⁴Associate Professor (Clinical) and Head, Outpatient Services and Mood Disorders Clinic, Department of Psychiatry, University of Sherbrooke, Sherbrooke, Quebec.

⁵Assistant Professor and Director, Mood Disorders Unit, Department of Psychiatry, University of Western Ontario, London, Ontario.

⁶Assistant Professor and Director, Mood Disorders Clinical Research Unit, Department of Psychiatry, University of British Columbia, Vancouver, British Columbia.

ADDRESS FOR CORRESPONDENCE: Dr SV Parikh, Clarke Institute of Psychiatry, 250 College Street, Toronto, ON M5T 1R8
email: parikhs@cs.clarke-inst.on.ca

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Section Three: Treatment of Mania, Mixed State, and Rapid Cycling

Treatment of Mania, Mixed State, and Rapid Cycling

Vivek Kusumakar, MBBS, FRCPC, MRCPsych¹, Lakshmi N Yatham, MBBS, FRCPC, MRCPsych², David RS Haslam, MSc, MD³, Sagar V Parikh, MD, FRCPC⁴, Raymond Matte, MD, FRCPC⁵, Peter H Silverstone, MD, FRCPC, MRCPsych⁶, Verinder Sharma, MD, FRCPC⁷

OBJECTIVES: TO SUMMARIZE THE QUALITY OF EVIDENCE FOR THE EFFICACY OF DIFFERENT BIOLOGICAL TREATMENTS IN MANIA, MIXED STATE, AND RAPID CYCLING AND TO PROPOSE GUIDELINES FOR TREATMENT OF THESE CONDITIONS.

METHOD: ARTICLES PUBLISHED ON TREATMENT OF ACUTE MANIA, MIXED STATES, AND RAPID CYCLING WERE REVIEWED AND RATED FOR QUALITY OF EVIDENCE USING PERIODIC HEALTH EXAMINATION GUIDELINES.

RESULTS: LITHIUM AND DIVALPROEX SODIUM ARE EFFECTIVE IN CLASSICAL PURE MANIA, WHEREAS DIVALPROEX SODIUM AND CARBAMAZEPINE ARE LIKELY MORE EFFECTIVE IN MIXED STATES. *OLANZAPINE AND RISPERIDONE HAVE BEEN REPORTED TO BE EFFECTIVE IN ACUTE MANIA. RECENTLY THE FOOD AND DRUG ADMINISTRATION (FDA) APPROVED OLANZAPINE FOR THE TREATMENT OF MANIA. PRELIMINARY DATA WITH OTHER ATYPICAL ANTIPSYCHOTIC DRUGS IN THE TREATMENT OF ACUTE MANIA ARE ENCOURAGING.* DIVALPROEX SODIUM IS LIKELY MORE EFFICACIOUS THAN CARBAMAZEPINE AND LITHIUM WHEN THE MANIA IS PART OF A RAPID-CYCLING COURSE. TYPICAL NEUROLEPTICS ARE EFFICACIOUS IN ACUTE MANIA, PARTICULARLY IN THE PRESENCE OF MARKED PSYCHOTIC SYMPTOMS. ATYPICAL NEUROLEPTICS CAN BE USEFUL IN REFRACTORY MANIA. SOME BENZODIAZEPINES DO HAVE ANTIMANIC EFFECTS, BUT THEY ARE INCREASINGLY BEING SHOWN TO HAVE USEFULNESS AS ADJUNCTS TO MOOD STABILIZERS OR NEUROLEPTICS RATHER THAN AS PRIMARY ANTIMANIC AGENTS. ELECTROCONVULSIVE THERAPY (ECT) IS AN

EFFICACIOUS AND BROAD-SPECTRUM TREATMENT.

CONCLUSIONS: MANIA CAN PRESENT WITH OR WITHOUT MOOD-CONGRUENT OR MOOD-INCONGRUENT PSYCHOTIC FEATURES AND AS PART OF A RAPID-CYCLING OR NONRAPID-CYCLING COURSE. MIXED STATE IS A COMMON PRESENTATION IN AN ACUTELY MANIC PATIENT. THE ACCURATE ASSESSMENT OF THESE ISSUES CAN SERVE AS A GUIDE IN DETERMINING TREATMENT OPTIONS AND CHOICES.

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KEY WORDS: MANIA, MIXED STATE, RAPID CYCLING, LITHIUM, DIVALPROEX SODIUM, CARBAMAZEPINE, NEUROLEPTICS, BENZODIAZEPINES, ELECTROCONVULSIVE THERAPY, *ANTIPSYCHOTICS*

Acute mania can be subdivided into classic pure mania, mania with mood-congruent or mood-incongruent psychosis, mixed state, and rapid cycling mania. Prior to embarking on treatment, it is important to confirm or rule out secondary mania (from, for example, Cushing's disease or syndrome, thyroid dysfunction, multiple sclerosis, corticosteroid use), mania induced by, exacerbated by, or comorbid with substance abuse, and antidepressant-induced mania (1-5). Treatment of the Cushing's disease or syndrome, downtitration and discontinuation of corticosteroids if medically permissible, and discontinuation of substance use or antidepressants may be sufficient to control the mania or reduce its intensity.

It is as yet unresolved whether antidepressant-induced mania is simply an adverse effect of the medication or an unmasking of underlying vulnerability to bipolar disorder. Most experts and experienced clinicians in the field tend to believe that the latter is the case. Mania can be induced not only by most antidepressant treatments but also by abrupt discontinuation of psychotropic medications in individuals with a predilection to bipolar disorder. Preventative strategies include using agents with a lower propensity for switch into mania or rapid cycling (6).

There is considerable evidence that sleep deprivation can provoke mood destabilization, particularly mania (7). Normalization of both the quantity of sleep and biorhythms can be useful in the

prevention of mood instability and as an adjunct to mood stabilizers in the treatment of hypomania and mania.

Recommendation 10: Conduct Thorough Medical Exam

Medical Evaluation of New Patients

Ideally, a medical evaluation and baseline investigations should be completed before the institution of biological treatment. In certain circumstances, however, because of a very acute clinical situation, treatment may have to begin prior to the completion of a medical evaluation and investigations.

Apart from a thorough medical examination, the following baseline investigations should be completed (*if clinically appropriate*): body weight and height, complete blood count including platelets; serum electrolytes; liver enzymes and serum bilirubin; prothrombin time and partial thromboplastin time; urinalysis and urine toxicology for substance use; serum creatinine, and/or, *if lithium will be used and if there is any personal or first degree family history of renal disease*, a 24-hour creatinine clearance; thyroid-stimulating hormone; electrocardiogram for patients over 40 years or if indicated otherwise; pregnancy test if relevant, *especially if divalproex will be used*.

While serum drug levels may be a helpful guide, dosing should be primarily based on clinically evident response and side effects and therapeutic window. During the acute phase, aim for the following serum levels: lithium 0.8 to 1.1 mmol/L. Evidence suggests that a lithium serum level of 0.8-1.2 mEq/L; valproic acid 400 to 700 mmol/L or valproic acid level of 50-150 ug/ml; for carbamazepine, there is no proven therapeutic level. Although there is no clear relationship between carbamazepine serum concentration and response, therapeutic concentrations for mania are reported to be 4-15 ug/ml. Note that lithium can be given in a single dose, as can slow-release carbamazepine, but divalproex should be given in 2 divided doses daily because of the absence of data on single daily dose treatment. Despite the lack of evidence for single dosing, the committee realizes that single daily dosing of divalproex is utilized in clinical practice (Zarate, Tohen, Narendran, et al., 1999). The clinician should consider divalproex administration via an oral loading dosage of 15-20 mg/kg/day during the acute manic phase of the illness (35). The new black box warning for divalproex does NOT represent a newly discovered increased risk for pancreatitis with this medication.

Serum levels should be repeated at the trough point (approximately 12 hours after the last dose). For lithium, serum levels

can be done about 5 days after most recent dose titration; for divalproex and carbamazepine, about 3 to 5 days after the most recent dose titration. Common practice is to establish about 2 consecutive serum levels in the therapeutic range during the acute phase. Thereafter, serum levels can be repeated every 3 to 6 months unless the clinical situation warrants otherwise. *It is common in clinical practice to measure serum levels annually in patients who are clinically stable and thought to be adherent to treatment.*

There is no evidence that blood counts and liver functions need to be done frequently (8,9). These investigations should be repeated about 4 weeks after commencement of treatment, and could be repeated once every 3 to 6 months thereafter. *It is common in clinical practice to measure serum electrolytes and hepatic enzymes annually in patients who are clinically and medically stable.* Closer monitoring, however, is required in children below the age of 10, seniors, medically ill patients, and patients on more than one medication. Clinical symptoms and signs of hematological, hepatic, cardiovascular, and neurological dysfunction are particularly valuable in predicting or timing investigations and remedial treatment (8,9). Thyroid and renal function, for lithium users, needs to be assessed annually. More extensive investigations should be performed only if there is a clinical indication.

Pharmacological Treatment of Acute Classical Pure Mania and Mixed State, with or without a Rapid-Cycling Course

The quality of evidence for different treatments as assessed by the Periodic Health Examination classification is presented in Table 1. Treatment recommendations for acute mania, mixed state, and rapid cycling are discussed below and illustrated in algorithms (10), reproduced courtesy of the Canadian Network for Mood and Anxiety Treatments (CANMAT) (Figures 1 and 2).

Recommendation 11: Lithium, Divalproex Sodium, Carbamazepine, and Other Agents

Table 1. Quality of evidence and recommendations for treatments as monotherapy: acute mania, mixed state, and rapid cycling*

<i>Primary Treatment^b</i>	<i>Quality of evidence^a</i>	<i>Working group Classification of recommendation^b</i>
Acute mania		
Lithium	1	A

Divalproex	1	A
Carbamazepine	1	B
Lamotrigine	na (1)	na (C)
Typical neuroleptic	1	B ^c
<i>Risperidone</i>	1	B
<i>Quetiapine</i>	3	C
<i>Clozapine</i>	2	B
<i>Ziprasidone</i>	1	C
Calcium channel blockers	1	C
ECT	1	B (A)
Clonazepam	1	C
Lorazepam	1	C
Gabapentin	na (3)	na (D)
<i>Topiramate</i>	3	C
<i>Olanzapine</i>	1	B

^aQuality of evidence rating system:

- 1 At least one randomized controlled trial.
- 2.1 Well-designed controlled trial without randomization.
- 2.2 Well-designed cohort or case-controlled studies, preferably multicentre or from more than one research group.
- 2.3 Very significant results from uncontrolled trials from more than one centre comparing results with and without intervention.
- 3 Opinions of respected clinical authorities based on clinical experience, descriptive studies, or reports of expert committees.

^bClassification of recommendations:

- A Good support for the intervention to be considered in clinical practice.
- B Fair support for the intervention to be considered in clinical practice.
- C Poor support for the intervention to be considered in clinical practice.
- D Fair support for the intervention to be excluded from clinical practice.
- E Good support for the intervention to be excluded from clinical practice.

*Combination treatment is described in more detail in the maintenance treatment section.

^cDespite the proven antimanic efficacy of typical neuroleptics, the working group was of the opinion that they should not be considered the sole or primary antimanic agents except in exceptional circumstances in view of the high risk of tardive dyskinesia with long-term use in this population. *Clinicians using this therapy should be*

mindful of EPS risks and of tardive dyskinesia.

^dSince the publication of the original guidelines, the committee decided to separate the different atypical antipsychotic drugs in the acute mania section as new information is available since the publication of these guidelines.

na = insufficient data to support a judgment at this time.

LITHIUM

Lithium has been shown to be superior to placebo and comparable in efficacy to antipsychotic and anticonvulsant agents (11-20). Pooled response rates from double-blind, placebo-controlled studies of lithium and acute mania showed significant improvement in 70% of patients. Bowden and others (13) demonstrated that 49% of patients treated with lithium displayed at least a 50% reduction in manic symptoms over a 3-week period. No other psychotropic medications were permitted in this study except the use of lorazepam as needed up to 4 mg/day and restricted wherever possible to the initial phase of treatment. The consensus is that lithium is superior to antipsychotics or benzodiazepines in normalizing the affective symptoms (*core manic symptoms*) but that neuroleptics have a more rapid onset of action and therefore may be more effective in the initial treatment of acute mania and in the acutely agitated patient (21-23). Failure to respond to lithium is associated with both the presence of a mixed state as well as a rapid-cycling current course of which the acute mania is a part (24-31). The presence of depressive symptoms during mania or immediately preceding mania may be predictive of response to divalproex and nonresponse to lithium (32) (Table 2).

Mixed State	Primary Treatment	
Lithium	1	C
Divalproex	1	B (A)
Carbamazepine	2.2	B
Lamotrigine	na (2.3)	na (B)
Typical neuroleptic	3	C
Atypical neuroleptic	3	C
Calcium channel blockers	3	D
ECT	3	C (B)
Clonazepam	3	D
Lorazepam	3	D
Gapapentin	na (3)	na (D)
Topiramate	na	na

Rapid Cycling	Primary Treatment	
Lithium	2.2	C
Divalproex	2.2	B
Carbamazepine	2.3	C
Lamotrigine	2(1)	B
Typical neuroleptic	3	D
Atypical neuroleptic	3	C
Calcium channel blockers	2.3	C
ECT	3	C
Clonazepam	3	D
Lorazepam	3	D
Gabapentin	1	C
Topiramate	3	C

DIVALPROEX SODIUM

Divalproex sodium and valproate have been shown to be effective in the treatment of acute mania in placebo crossover trials (33) and compared with lithium and placebo in a randomized parallel-group trial (34). Divalproex sodium is preferred in clinical practice because it has fewer gastrointestinal side effects than sodium valproate or valproic acid. Bowden and others reported that divalproex was as effective as lithium and both were significantly better than placebo in the treatment of acute mania (13). Compared with the limited effect produced by lithium in rapid-cycling bipolar type I disorder patients, divalproex was effective in these patients in addition to those who had a nonrapid-cycling course. As previously mentioned, in Bowden and others' study (13), no other psychotropic medications were used other than lorazepam up to 4 mg/day as an adjunct to both interventions, primarily during the initial phase of treatment. The effectiveness in clinical practice would be expected to be enhanced by the use of adjunctive agents like benzodiazepines or neuroleptics. Divalproex sodium is effective in rapid-cycling patients as well as in more than 50% of patients in a mixed state. The presence of depressive symptoms during mania or immediately preceding a manic episode may be predictive of response to divalproex and nonresponse to lithium (32) (see Table 2). *The number of previous affective episodes appears to be predictive of response or nonresponse to divalproex and lithium (Swann, Bowden, Calabrese, et al., 1999). For patients who had experienced 10 or more episodes, response to divalproex but not lithium in a long-term maintenance study was found to be significantly better than placebo.*

In this trial, previous response to lithium predicted superior response to lithium than to divalproex or placebo. Although clinicians have commonly justified the use of neuroleptics because of their early onset of action, there is growing evidence that oral loading doses of 15 to 20 mg/kg/day of divalproex can produce rapid onset of antimanic action comparable to that of haloperidol but with fewer side effects (35).

CARBAMAZEPINE

There are numerous double-blind studies to support the efficacy of carbamazepine in the treatment of acute mania (36-42). The majority of these studies, however, are confounded by the concurrent administration of antipsychotics and/or lithium (43). This is important to note because there is reported synergistic action when carbamazepine and lithium are combined in situations where patients fail to respond to either medication on its own (44). Pooled data support that the overall response rate of 50% in the treatment of acute mania is no different from that for divalproex sodium and lithium (45) (see Table 2). Carbamazepine is reportedly effective in mixed state, but its value in rapid cycling is being increasingly questioned (46).

LAMOTRIGINE, GABAPENTIN, AND TOPIRAMATE

There is insufficient evidence at this stage with both lamotrigine and gabapentin to support their efficacy as first-line agents in acute pure mania. There are case reports and small case series, however, that support the value of lamotrigine in rapid-cycling states (47). Controlled double-blind studies with both compounds are currently under way. At present, these compounds are used only in refractory mania, mixed states, or rapid cycling. *Since the publication of these Canadian guidelines, additional information on the efficacy of lamotrigine and gabapentin has become available. Lamotrigine was shown to be effective in the treatment of hypomanic, manic, mixed and depressive symptoms in a 48-week open-label prospective study involving 75 treatment-refractory bipolar I or II disorder patients (Bowden, Calabrese, McElroy, et al., 1999). Lamotrigine was used as monotherapy in 15 subjects and as adjunctive therapy in 60 subjects in this trial. The most common drug-related adverse events in this study were dizziness, tremor, somnolence, headache, nausea, and rash. Rash was the most common adverse event resulting in drug discontinuation (9% of patients); one patient developed a serious rash and required hospitalization. Lamotrigine monotherapy was shown to be effective for mania in a very small 4*

week, double blind, lithium controlled trial (Ichim, Berk, & Brook, 2000). As there were only 15 subjects per arm in this trial, we consider that this is insufficient evidence to rate the evidence for monotherapy in mania as a 1. Lamotrigine monotherapy was effective in rapid cycling patients and superior to topiramate and placebo in a small double blind crossover trial by Frye and colleagues.

Although early open studies suggested that gabapentin may possess antimanic, antidepressant and mood stabilizing properties, controlled trials have not found gabapentin to be superior to placebo for acute treatment of mania, mixed states or rapid cycling (unpublished, presented at a scientific meeting, Pande et al., 2000; Frye et al., 2000). Gabapentin has recently been found in two double-blind studies to be ineffective as an adjunctive or monotherapy treatment of the acute phase of mania, mixed states or depression of bipolar disorder [Pande et al., 2000]. This implies that gabapentin is probably not effective in acute mania. Gabapentin monotherapy was found in a double blind trial by Frye and colleagues to be no better than placebo in treatment refractory rapid-cycling bipolar I and bipolar II patients.

Recent interest has been generated with the antiepileptic topiramate. Preliminary data using topiramate in bipolar disorder suggest that this antiepileptic may possess mood-stabilizing and weight loss properties (Marcotte, 1998; Chegappa, Rathore, Levine, et al., 1999). In the retrospective chart review by Marcotte, open-label topiramate was added to current treatment in 58 patients who were refractory to conventional mood stabilizers. 44 out of 58 patients had rapid cycling bipolar disorder and most showed marked or moderate improvement using descriptive statistics. However, controlled data with topiramate in acute mania have not yet been published.

Figure 1. Acute Mania and Mixed State.

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Figure 2. Rapid Cycling.

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BENZODIAZEPINES

Lorazepam and clonazepam have been the most studied benzodiazepines in acute mania, and controlled studies support the conclusion that both agents are useful in the treatment of acute mania (48-52). Bradwejn and others, in a double-blind comparison of the effects of clonazepam and lorazepam in acute mania without the use of other psychotropic agents over a 14-day period, reported that 61% of patients responded positively to lorazepam treatment, with 38.5% achieving remission (48). This compared with only an 18.2% response rate and a 0% remission rate in patients treated with clonazepam alone. Clinicians have raised concerns about the possibility of exacerbating disinhibition in acute mania with the use of benzodiazepines on their own, but they have been shown to be useful adjuncts with mood stabilizers in the treatment of acute mania (52,53). Bowden and others demonstrated the efficacious use of lorazepam as an adjunct for behavioural suppression when used with either lithium or divalproex (13). Collectively, studies suggest that benzodiazepines are effective in place of or in conjunction with a neuroleptic in sedating the acutely agitated manic patient while waiting for the effects of other primary mood-stabilizing agents to become evident. Lorazepam has, by virtue of its multiple routes of administration and favourable intramuscular absorption, become a useful choice. Further, both lorazepam and clonazepam are preferable to neuroleptics if the possibility of precipitating extrapyramidal symptoms and acute dystonias is unacceptable. An obvious disadvantage of benzodiazepines are their propensity for dependence and, in patients with comorbid substance use disorder, the potential to induce another substance use disorder is a cause for concern. Benzodiazepines also have the potential to cause either dysphoria or disinhibition in some patients (54,55). A recent report suggests that clonazepam augmentation may not prove useful in the maintenance treatment of bipolar disorder (ref).

Table 2. Predictors of response or nonresponse for 3 treatments

Agent	Predictors of response	Predictors of nonresponse
Lithium	Acute mania	Mixed state
	Family history of response	Depression-mania-euthymia course
	Mania-depression-euthymia course	Rapid cycling
	Bipolar disorder, 3 or fewer cycles per year	<i>More than 10 lifetime episodes</i>
Divalproex sodium	Acute mania Rapid cycling Mixed state Secondary mania	
Carbamazepine	Acute mania Mixed state Secondary mania	Rapid cycling

Recommendation 12: Typical Neuroleptics

TYPICAL NEUROLEPTICS

Controlled studies have shown that neuroleptics are superior to placebo in the treatment of acute mania (23). Studies comparing lithium with neuroleptics (chlorpromazine or haloperidol) usually suggest that, while lithium may be superior to neuroleptics for the specific normalization of mood, neuroleptics often have a quicker onset of action (17,19,23,56-61).

Although clinicians have commonly justified the use of neuroleptics because of their early onset of action, there is growing evidence that oral loading doses of 15 to 20 mg/kg/day of divalproex can produce rapid onset of antimanic action and an antipsychotic response comparable to that of haloperidol but with fewer side effects (35). Neuroleptics carry the risk of causing extrapyramidal symptoms and acute dystonia, as well as an increased risk of tardive dyskinesia with long-term use in patients with a mood disorder.

Recommendation 13: Atypical Neuroleptics, ECT, Channel Blockers

ATYPICAL NEUROLEPTICS

Both risperidone and clozapine have antimanic properties as reported by a variety of investigators in uncontrolled studies (23,62-70). *Since the publication of these Canadian guidelines, olanzapine has been approved by the FDA for use in acute mania and the role of antipsychotic drugs in bipolar disorder has been reviewed (Tohen & Zarate, 1998).* Calabrese and others demonstrated in an open trial that clozapine was effective in both pure bipolar disorder and in mania related to schizoaffective disorder that was resistant to front-line antimanic treatments (71). Despite the difficulty in obtaining clozapine for patients without schizophrenia in many provinces in Canada and the risk of hematological side effects, there is growing evidence that clozapine may be an appropriate mood-stabilizing agent in refractory mania. This intervention may also have a role in the treatment of refractory bipolar depression (65,70,72).

There is one report of risperidone monotherapy in acute mania. In this small double blind placebo controlled trial reported by Segal and colleagues. 45 subjects were randomized to receive risperidone or lithium monotherapy. There was no difference in effectiveness between the groups, although the study had very low power to detect a difference between the groups. Importantly, no induction of mania was seen in the risperidone group. The interpretation of larger studies of risperidone use in acute mania are complicated by the inclusion of patients with bipolar disorder who were already receiving mood stabilizers. The dose of risperidone in these studies varied from 1 to 6 mg/day. There are some data to suggest that risperidone, especially when given in higher doses of 6 to 8 mg/day, may induce or exacerbate manic symptoms (73). Systematic studies are under way with this compound in acute mania. A recent double-blind, placebo-controlled study found risperidone to be effective as an adjunctive therapy to mood stabilizers in acute mania (unpublished findings presented at a scientific meeting, Sachs & Risperidone Study Group, 1999).

Olanzapine monotherapy has recently been reported to be effective in the treatment of acute mania and has received FDA approval for this indication. In this study, 49% of patients treated with olanzapine displayed at least a 50% reduction in manic symptoms over a 3-week period (Tohen, Sanger, McElroy, et al., 1999; Tohen, Jacobs, Grundy, et al., 2000). The long-term efficacy and safety of olanzapine as a mood stabilizer has not yet been estab-

lished, and further evidence is needed before olanzapine can be considered first line monotherapy for mania (McElroy & Keck, 2000). The clinician should take this into account when deciding on long-term maintenance treatment with olanzapine.

Initial reports suggest that quetiapine as an adjunctive treatment may have a role in bipolar disorder; however, controlled studies are lacking (Ghaemi & Katzow, 1999; Zarate, Rothschild, Madrid, et al., 2000)

ECT

In a review of ECT in acute mania, Mukherjee and others found that 80% of patients showed marked clinical improvement (74). Many manic patients respond relatively rapidly to ECT when compared with their response to mood stabilizers (75). The attractiveness of ECT is also that patients who are treatment-refractory to pharmacotherapy often respond to ECT (76). There is little evidence that manic patients require a high frequency or prolonged course of treatments to respond to ECT. The seizure threshold appears to be lower in manic patients than in depressed patients. The majority of studies reviewed by Mukherjee and others reported that bilateral ECT was superior to unilateral ECT in the treatment of acute mania (74). This issue requires further study, although clinical consensus appears to be that bipolar patients do better with bilateral ECT. The presence of pregnancy, manic delirium with severe hypothermia, neuroleptic malignant syndrome, catatonia, and some comorbid general medical conditions may be primary indications for ECT, both in view of its effectiveness and its high margin of safety in these situations (77). Despite a lack of rigorous studies, clinical experts agree that ECT is useful both in rapid-cycling and mixed state illness as well as in refractory states with these conditions. Lithium should be temporarily discontinued or the dosage dramatically reduced when using ECT to avoid the rare but potentially fatal associated complications of delirium and status epilepticus (78-80). Benzodiazepine and anticonvulsant administration should be minimized or discontinued briefly to optimize seizure duration and threshold (81).

CALCIUM CHANNEL BLOCKERS AND THYROXINE

Bowden has stated that the studies with calcium channel blockers are small in number, flawed in design, and mixed in results (82). Although in initial studies, verapamil was reported to be superior to placebo (83,84), the only randomized placebo-controlled study reported no differences in outcome between verapamil and

placebo treatment (85). In addition, one study has shown that verapamil may worsen or precipitate depression (86). Verapamil is weakly lipophilic and probably does not reach the central nervous system in adequate concentrations. Several other calcium channel blockers are highly lipophilic, and nimodipine, a dihydropyridine that blocks the calcium channel directly, has been reported to be efficacious in small case series of rapid-cycling patients, particularly the ultrarapid-cycling variety. There is no conclusive evidence of the value of thyroxine supplementation in rapid-cycling disorder except where there is proven hypothyroidism.

PSYCHOTIC MANIA

Available studies indicate that mood-congruent grandiose delusions are probably the most common type of psychotic symptoms in mania (87). Mood-incongruent psychotic symptoms are also commonly seen in acute mania (87,88). Psychotic symptoms appear to be commonly associated with increasing severity of an acute manic episode. McElroy and others (23) and Tohen and colleagues (89) conclude that there is inconsistent evidence as to whether psychotic mania is associated with a similar or poorer outcome compared with nonpsychotic mania. There is no conclusive evidence to suggest that mood-incongruent or bizarre psychotic symptoms and formal thought disorder are associated with poorer outcome when seen in acute mania. Persistent psychotic symptoms present in the continuation and maintenance phases of the illness, however, are associated with relatively poorer prognosis. No controlled study has prospectively examined the response of patients with acute mania to antipsychotics, mood stabilizers, or an antipsychotic plus mood stabilizer combination according to the presence or absence of psychotic symptoms.

It is unknown, therefore, whether patients with psychotic mania truly require adjunctive neuroleptics for optimal response more often than those patients with nonpsychotic mania (23). A second issue is that typical antipsychotics may exacerbate bipolar depressive symptoms both acutely and over the long term (90-94). Limited evidence suggests that the newer atypical neuroleptics do not provoke bipolar depression.

Common practice has been to treat acute psychotic mania, especially if accompanied by severe agitation, with neuroleptic medication initially, in order to hasten and maximize the treatment response. Preliminary studies suggest that benzodiazepines may be as effective as neuroleptics in reducing agitation when used adjunctively with a mood stabilizer to treat acute mania (51). Further, oral loading with divalproex sodium (15 to 20 mg/kg/day) may

produce rapid onset of an antimanic and antipsychotic response comparable to that of haloperidol and with minimal side effects in the initial treatment of acute psychotic mania in some bipolar patients (35). The use of oral loading with divalproex, which may have an early onset of action superior to lithium, may obviate the need for antipsychotic medication treatment in many instances. As reported earlier, the newer atypical neuroleptics like risperidone, *olanzapine* and clozapine have also been reported to be useful in patients refractory to traditional mood stabilizers, although risperidone in doses above 6 mg may exacerbate mania. *Exacerbation of acute mania has not been observed in controlled trials of risperidone or olanzapine in mania.*

In summary, neuroleptic medications offer advantages and disadvantages. Advantages include early onset of action, parenteral administration in patients refusing oral medication, specific antipsychotic effects in patients with persistent psychotic symptoms, and clinical familiarity with their use. The disadvantages and limitations include extrapyramidal symptoms, acute dystonias, tardive dyskinesia seen with typical neuroleptics, hematological complications with clozapine, and the possibility of exacerbation of mania with doses of risperidone over 6 mg/day.

Although inconsistencies exist, considerable data suggest that neuroleptic treatment in acute mania with psychosis, in general, is not associated with better outcome. McElroy and others have stated that the acute and maintenance treatment of psychotic mania should be similar to that of nonpsychotic mania, with mood stabilizers being the primary agents (23). Typical neuroleptics should be reserved for patients with severe acute agitation, those who refuse oral medication, those who present mood-incongruent or persistent psychotic symptoms, and those who are inadequately responsive to, intolerant of, or noncompliant with mood stabilizers. By contrast, atypical neuroleptics like risperidone, *olanzapine*, *ziprasidone* and clozapine need to be studied further, *and* may be superior choices to typical neuroleptics in acute psychotic mania, *non-psychotic mania*, and refractory mania.

Summary of Evidence and Recommendations

Table 1 summarizes the quality of available evidence (using the Periodic Health Examination classification) for the treatment of acute mania, mixed state, and rapid cycling, as well as the classification of recommendations of the working group for use in clinical practice. The classification of recommendations is the product of a consensus process and reflects a global impression based on the quality of evidence for efficacy, adverse effects, tolerability, and acceptability for the patient.

TREATMENT OF ACUTE MANIA AND MIXED STATES (SEE FIGURE 1)

In acute mania, it is common practice to begin treatment with a mood stabilizer, either lithium or divalproex. In mixed mania, divalproex and carbamazepine are the drugs of choice. The principle is to use the medication that has antimanic efficacy and is likely to be used for prophylaxis. In moderate to severe mania, there is often a need to achieve rapid stabilization. This can be accomplished by the use of a loading dose of 20 mg/kg/day of divalproex, the use of lorazepam or clonazepam in doses from 2 to 12 mg/day, and/or, where there is severe behavioural disturbance and marked psychosis, the use of a neuroleptic or ECT. Both typical and atypical neuroleptics have specific, antimanic effects. Neuroleptics should be discontinued after the patient has been stabilized, usually about 2 weeks into treatment unless there are persistent and/or mood-incongruent psychotic symptoms. Behaviour suppressors like lorazepam and clonazepam have been used successfully as adjuncts instead of neuroleptics (53). Neuroleptic use is indicated in the long term if there is persistent or mood-incongruent psychosis. In such cases, it is important to taper and stop antidepressants or other manicogenic agents and to stabilize sleep patterns. Substance and alcohol use should be discontinued.

If the mania or mixed state is refractory to treatment, there should be a reassessment of the possibility of an underlying treatable medical cause. Any medical condition or substance abuse should be treated. If these are not present, the clinician may add a second mood stabilizer while concurrently evaluating the need for ECT, depending on the clinical situation. The combination of 3 mood stabilizers (lithium, divalproex, and carbamazepine) and an atypical neuroleptic (*olanzapine 10-20 mg/day, or risperidone, in doses below 4 mg/day, or clozapine at therapeutic doses*) may be tried sequentially. The addition of a calcium channel blocker or a novel agent like lamotrigine, *topiramate* or gabapentin may also be considered.

It is usually sufficient to measure serum medication levels no more frequently than once a week in the acute phase. Serum medication levels should be repeated until 2 consecutive levels have been obtained in the therapeutic range. After baseline investigations, the monitoring of bodily systems should be conducted as clinically indicated.

TREATMENT OF RAPID-CYCLING BIPOLAR DISORDER (SEE FIGURE 2)

Rapid-cycling bipolar disorder may be a phase of the disorder or, in some cases, a type of disorder. It is important to stabilize sleep and to reduce or stop the use of caffeine, nicotine, alcohol, and other substances *in an effort to stabilize cycling*. Antidepressant medications, particularly tricyclics, may provoke rapid cycling. *Clinicians should consider discontinuing these medications when clinical presentation permits*. Care should be taken to discontinue any psychotropic agents gradually, never abruptly.

Divalproex sodium is the first treatment of choice *in rapid cycling bipolar disorder*. In partial or nonresponders, lithium or carbamazepine may be added to the divalproex. Further on, the combination of 3 mood stabilizers or ECT could be tried. Lamotrigine, *topiramate*, gabapentin, nimodipine, or thyroxine in addition to an established mood stabilizer may be used. Clozapine should be considered in the truly refractory patient.

Clinical Implications

- Although lithium is a tried and tested medication with proven efficacy in acute mania, *and is a first line treatment choice for classic mania*, divalproex sodium likely has a broader-spectrum efficacy, and carbamazepine can be an alternative in certain clinical situations.
- There are important but limited roles for *conventional and atypical* neuroleptics, benzodiazepines, and ECT.

Limitations

- The evidence from well-designed, double-blind controlled studies with adequate numbers of patients is mainly limited to lithium and divalproex. *Recently, olanzapine in a double blind, placebo controlled study was shown to be effective and safe in the treatment of acute mania.*
- There are no methodologically sound studies in mixed state and rapid cycling.
- There is sparse evidence for the efficacy of atypical neuroleptics and novel agents.

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¹Associate Professor and Head, Division of Child and Adolescent Psychiatry; Director, Mood Disorders Group, Department of Psychiatry, Dalhousie University, Halifax, Nova Scotia.

²Assistant Professor and Director, Mood Disorders Clinical Research Unit, Department of Psychiatry, University of British Columbia, Vancouver, British Columbia.

³Resident, Department of Psychiatry, Dalhousie University, Halifax, Nova Scotia.

⁴Assistant Professor, Department of Psychiatry, University of Toronto; Head, Bipolar Clinic, Clarke Institute of Psychiatry, Toronto, Ontario.

⁵Associate Professor (Clinical) and Head, Outpatient Services and Mood Disorders Clinic, Department of Psychiatry, University of Sherbrooke, Sherbrooke, Quebec.

⁶Associate Professor, Department of Psychiatry, University of Alberta, Edmonton, Alberta.

⁷Assistant Professor and Director, Mood Disorders Unit, Department of Psychiatry, University of Western Ontario, London, Ontario.

ADDRESS FOR CORRESPONDENCE: Dr. V. Kusumakar, Department of Psychiatry, Dalhousie University, IWK-Grace Health Centre, 5850 University Avenue, Halifax, NS B3J 3G9
email: vkusumakar@usa.net

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Section Four: Bipolar Depression: Treatment Options

Bipolar Depression: Treatment Options

Lakshmi N Yatham, MBBRS, FRCPC, MRCPsych¹, Vivek Kusumakar, MBBS, FRCPC, MRCPsych², Sagar V Parikh, MD, FRCPC³, David RS Haslam, MSc, MD⁴, Raymond Matte, MD, FRCPC⁵, Verinder Sharma, MBBS, FRCPC⁶, Sidney Kennedy, MD, FRCPC⁷

OBJECTIVE: TO REVIEW STUDIES ON TREATMENTS FOR BIPOLAR DEPRESSION AND MAKE RECOMMENDATIONS FOR PRACTISING CLINICIANS TREATING PATIENTS WITH BIPOLAR DEPRESSION.

METHOD: STUDIES THAT EXAMINED VARIOUS TREATMENTS FOR BIPOLAR DEPRESSION WERE EVALUATED AND RATED FOR EVIDENCE OF EFFICACY USING PERIODIC HEALTH EXAMINATION CRITERIA. THE RATING FOR CLASSIFICATION OF RECOMMENDATION FOR AN INTERVENTION WAS MADE TAKING BOTH THE EFFICACY AND SIDE EFFECTS INTO CONSIDERATION.

RESULTS: MOOD STABILIZERS, CYCLIC ANTIDEPRESSANTS, MONOAMINE OXIDASE INHIBITORS (MAOIS), AND ELECTROCONVULSIVE THERAPY (ECT) ARE ALL EFFECTIVE IN TREATING BIPOLAR DEPRESSION. ALMOST ALL ANTIDEPRESSANT TREATMENTS WITH THE EXCEPTION OF MOOD STABILIZERS HAVE BEEN REPORTED TO INDUCE A MANIC-HYPOMANIC SWITCH AND RAPID CYCLING.

CONCLUSIONS: MOOD STABILIZERS, LITHIUM IN PARTICULAR, ARE RECOMMENDED AS THE FIRST-LINE TREATMENT. ADDITION OF A SECOND MOOD STABILIZER OR A CYCLIC ANTIDEPRESSANT WOULD BE AN APPROPRIATE NEXT STEP. NEWER AGENTS SUCH AS LAMOTRIGINE OFFER CONSIDERABLE PROMISE IN TREATING BIPOLAR DEPRESSED PATIENTS.

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KEY WORDS: BIPOLAR DEPRESSION, LITHIUM, ANTIDEPRESSANTS, MANIA

Bipolar depression is defined as the occurrence of a major depressive episode in a patient who has had at least one hypomanic or manic episode (1). This condition affects approximately 1% of the general population (2). Depression may be the first affective episode in more than 50% of patients with bipolar disorder (3). In such cases, factors such as bipolar family history, presence of psychotic features, chronicity of depressive episode, early age at onset, and presence of atypical symptoms, such as hypersomnia, hyperphagia, and a significant psychomotor retardation, may be helpful in predicting a bipolar course (4,5).

This condition is associated with considerable morbidity and mortality. The mean duration of bipolar depressive episodes is considerably longer than manic episodes, and more than 20% of bipolar depressive episodes run a chronic course (6). Despite this, few controlled clinical trials have rigorously examined the effectiveness of specific interventions in treatment of bipolar depression. Most of our current state of knowledge about treatment of depression is derived from clinical trials that systematically excluded bipolar depressed patients. Although no consistent biochemical abnormalities have emerged between unipolar and bipolar depressed patients (7), several other lines of evidence pertaining to symptoms (8-10), course of illness (11-14), and response to treatment (15,16) have accumulated over the past few decades, supporting the bipolar-unipolar dichotomy. Recent long-term follow-up studies examining the course and outcome (17) and the stability of polarity distinction (5) provided further support for the unipolar-bipolar distinction. Effective treatments for unipolar depressed patients, therefore, may or may not be effective for bipolar depressed patients.

In view of the concerns about generalizability of data, the evidence used to formulate treatment recommendations in this paper was based mainly on studies of bipolar depressed patients. In cases where data were not available on bipolar depressed patients, data from studies of unipolar depressed patients were used, mainly out of necessity. This necessity is less problematic if the limitations of generalization of data are kept in mind. Apart from a potential difference in the effectiveness of antidepressant treatments for 2 conditions, the treatment of bipolar depression is often complicated by the fact that many antidepressant medications have been reported to induce a manic or hypomanic switch and rapid cycling in this population (18-22). This was the paramount issue in developing an algorithm for the treatment of bipolar depression.

Although extensive data are available on the efficacy of psychosocial treatments in unipolar depression, little is known about their efficacy in bipolar depression. This review will briefly touch on the role of such treatments (see the article by Parikh and others [xxx for

page 74S] for a more detailed discussion) and then examine the efficacy of various medications in treating bipolar depression. We will then suggest clinical recommendations and an algorithm for a clinician to treat patients with bipolar depression.

Recommendation 14: Psychosocial Interventions

Psychosocial Interventions

Bipolar disorder is associated with severe occupational and social deficits. Such deficits may represent residual temperamental disturbances of a “subaffective” nature and/or the psychological sequelae of illness episodes (for example, shame, low self-esteem) (23,24). Mild depressive symptomatology may be successfully treated with cognitive-behavioural or interpersonal therapy, most often in combination with pharmacological interventions. Each of these psychosocial interventions requires some tailoring to the needs of individual patients. Controlled experimental trials of “manualized” interventions (that is, written guidelines for how and when treatment should be administered) are currently being conducted (23). These standardized approaches may optimize the implementation of psychosocial interventions by providing practical and reproducible approaches that have empirically proved effectiveness in bipolar patients. The quality of evidence for psychotherapy was rated as “3,” and recommendation for clinical practice was determined to be “C” (Table 1).

Recommendation 15: Pharmacological Treatments

Pharmacological Treatments

LITHIUM

An open study (25) and 7 of 8 double-blind, placebo-controlled crossover studies (15,16,26-31) reported lithium to be superior to placebo in treating bipolar depression. In these trials, response rates to lithium ranged from 64% to 100%, and relapse of depressive symptoms ranged from 38% to 70% when switched to placebo. In the only double-blind, placebo-controlled parallel-group trial that compared lithium to imipramine, reductions in mean depressive scores were 32% and 58% for lithium and imipramine, respectively (32). In summary, clinical trials suggest that lithium is superior to placebo in treating bipolar depression, but the efficacy of lithium in comparison to antidepressants remains uncertain. Overall, the quality of the evidence for lithium treatment rates as “1,” and the

classification of recommendations was determined to be “A” (see Table 1).

MAOIs

Double-blind trials involving subjects with anergic bipolar depression have demonstrated response rates of approximately 75% and 50% with tranylcypromine and imipramine interventions, respectively (33-35). Fewer dropouts and lower switch rates were noted in the tranylcypromine-treated group compared with imipramine-treated subjects. Phenelzine has been reported to be effective in case studies of patients with bipolar depression (36). In the only double-blind trial that examined the efficacy of moclobemide, a reversible inhibitor of monoamine oxidase A, 53% of patients with bipolar depression responded compared with 60% in the imipramine-treated group (37). MAOIs have been reported to cause a switch of mood, but hypomania is more common than mania. Overall, the quality of evidence for MAOI treatment is “1,” and the classification of recommendations was set at “D” in view of the concern about a manic or hypomanic switch. The use of MAOIs in combination with a mood stabilizer, however, received a “B”-level classification.

HETEROCYCLIC ANTIDEPRESSANTS

A number of double-blind trials investigating the efficacy of the tricyclic antidepressant (TCA) imipramine reported an average response rate of 55% (34,35,37-38). The response rate in fluoxetine-treated subjects may be marginally higher than in those treated with TCAs (38,39), with switches reported in both groups. Case reports, as well as results of a double-blind trial, suggest that bupropion may be effective in treatment of bipolar depressed patients (40,41). Although no study directly compared the switch rate in patients on TCAs with those on selective serotonin reuptake inhibitors (SSRIs), data from clinical trials suggest that TCAs more commonly cause a switch into mania (more than 10%) than SSRIs (less than 5%) (21), and TCAs more commonly induce rapid cycling (22). In view of this, there is growing consensus that TCAs should be avoided in bipolar depression. As depression is a common first mood disorder episode in early-onset bipolar disorder, and because there is little evidence for the efficacy of TCAs in adolescents,

continued on page 73

Table 1. Quality of evidence and recommendations for treatments: bipolar depression

Treatment	Quality of evidence ^a	Working group classification of recommendation ^b	
Psychotherapy	3	C	
Lithium	1	A	
Divalproex	2.3	C	
Carbamazepine	1	C	
<i>Lamotrigine</i> ^c	<i>1</i>	<i>C (B)</i>	
		Alone	With Mood Stabilizer
TCA's	1	D	C
MAOIs	1	D	B
SSRIs	1	D	B
Bupropion	1	D	B
Serotonergic noradrenergic reuptake inhibitors (SNRIs)	3	D	C
ECT	2.3	B (A)	B
Light therapy	3	D	C
Sleep deprivation ^d	3	D	C
<i>Gabapentin</i>	<i>NA</i>	<i>D</i>	<i>C</i>

^aQuality of evidence rating system:

- 1 At least one randomized controlled trial.
- 2.1 Well-designed controlled trial without randomization.
- 2.2 Well-designed cohort or case-controlled studies, preferably multicentre or from more than one research group.
- 2.3 Very significant results from uncontrolled trials from more than one centre comparing results with and without intervention.
- 3 Opinions of respected clinical authorities based on clinical

experience, descriptive studies, or reports of expert committees.

^bClassification of recommendations:

- A Good support for the intervention to be considered in clinical practice.
- B Fair support for the intervention to be considered in clinical practice.
- C Poor support for the intervention to be considered in clinical practice.
- D Fair support for the intervention to be excluded from clinical practice.
- E Good support for the intervention to be excluded from clinical practice.

‘Unclear evidence of lamotrigine’s mood stabilizing properties at the time of the committee’s revision. Lamotrigine was left in this section because it is an anticonvulsant.

^dNot recommended by the committee.

TCAs should be avoided. The quality of evidence concerning these treatment interventions is strong: “1.” The working group classification of recommendations was “D” in view of the concern about a switch into mania or hypomania. When used in combination with a mood stabilizer, however, the rating is “B” for SSRIs and bupropion, and it is “C” for TCAs. *A recent double-blind study in acute bipolar depression found that there was no advantage of adding a second mood stabilizer versus an antidepressant (paroxetine) to an initial mood stabilizer; both groups showed similar and significant improvement in depressive symptoms during the 6-week trial. There were, however, significantly more noncompleters in the group being treated with the two mood stabilizers (Young, Jeff, Robb, et al., 2000).*

ANTICONVULSANTS AND BENZODIAZEPINES

Double-blind, placebo-controlled trials report an approximate 70% response rate to carbamazepine and a 50% relapse rate with placebo substitution in the treatment of bipolar depression (42-44). In patients with rapid-cycling bipolar disorder, 47% had antidepressant response to divalproex sodium in an open prospective trial (45). Despite the optimistic report of a small case series (46), there is little robust current evidence to support the use of divalproex in acute bipolar depression. In 2 large open-labelled series from at least 3 centres (47,48), lamotrigine has been reported to be a promising agent in the treatment of bipolar depression, although in a signifi-

cant number of cases, lamotrigine was added to either divalproex or lithium. Double-blind controlled studies are currently under way to test the efficacy of lamotrigine in bipolar depression. *Recently, one large double-blind randomized placebo controlled study found that lamotrigine 200 mg/day demonstrated significant antidepressant efficacy in treating acute bipolar depression compared to placebo (Calabrese, Bowden, Sachs, et al., 1999).* There is no published literature on gabapentin, although studies are currently being conducted with this compound. *There have been no adequately controlled data with gabapentin in acute bipolar depression. There is no data to support the use of gabapentin in the acute depressive phase of bipolar disorder (Table 1) (Frye, Ketter, Osuch, et al., 1999).*

Although a double-blind trial has demonstrated a response rate of 60% in adinazolam-treated bipolar depressed patients, the use of this agent as an antidepressant is not recommended given the risk of abuse potential and dependency and the availability of other effective agents with a more favourable risk-to-benefit profile (49). *Adinazolam is not currently available in the United States.* There is little or no evidence that other benzodiazepines have any efficacy in bipolar depression. Overall, the quality of evidence for carbamazepine is "1" and for divalproex and lamotrigine is "2.3." *In light of recent data, the quality of evidence for lamotrigine is now "1" and the recommendation would be "B".* The working group recommended a classification for all 3 agents of "C," but the recommendation would be "B" for lamotrigine if used in combination with another mood stabilizer such as lithium or divalproex sodium.

MISCELLANEOUS TREATMENTS

A small double-blind trial reported levosulpiride (*currently not available in the United States*) to have a comparable response rate (90%) to that of amitriptyline in bipolar depressed patients (50). Much less robust evidence of varying rates of response to dopamine receptor agonists (51,52), total (53) and partial sleep deprivation (54,55), and light therapy (56) have also been reported. Dopamine receptor agonism has been associated with a high switch rate into hypomania or mania (51,52). Clozapine has been reported to be effective in bipolar depression in multiple case series studying refractory bipolar depression (57). Studies with olanzapine are currently being conducted, but as yet there is no published literature with this compound. *Studies of omega three fatty acids are in progress to better characterize this potentially promising therapy.*

Recommendation 16: Pharmacological Augmentation, Combinations, and ECT

Pharmacological Augmentation and Combinations

Lithium augmentation of TCA- (58) and carbamazepine-resistant patients (59) is reported to have led to marked improvement in 36% and 46% of study subjects, respectively. The use of TCAs is not advisable, however, because they carry a risk of switch into mania and induction of rapid cycling. Although the superiority of bupropion augmentation of mood stabilizers has been inconsistent, conversion of nonresponder to responder rates has exceeded 60% in 2 open studies (60,61) and a double-blind trial (41). Further, bupropion appears to have a lower risk of switching patients into mania or accelerating cycles *but this conclusion is tentative and based on very few patients (41)*. Case reports involving subjects receiving antidepressants suggest that carbamazepine administered concurrently with lithium may be effective in lithium-resistant bipolar depressed patients (62,63). *More information on combination treatment is in the maintenance section.*

ECT

Several open prospective trials and a number of retrospective studies have reported the efficacy rate of ECT in bipolar depression to be at least 50% and as high as 100% (64-69).

Rate of switch to elevated mood of bipolar depressed patients treated with ECT appears equivalent to that associated with conventional antidepressant treatment (18). ECT is a bimodal treatment, however, and continuing with the course of ECT can produce euthymia. The ratings for quality of evidence and treatment recommendations were “2.3” and “B” for ECT.

Switch into Hypomania or Mania during Treatment for Depression

ECT is no more likely than antidepressants to precipitate a switch into hypomania or mania and to induce rapid cycling, whereas SSRIs may have decreased rates of switch compared with TCAs (18,21). A recent study reported that mania in one-third and rapid cycling in one-fourth of refractory bipolar patients was attributable to antidepressants and not to the expected course of illness (70). There is a growing clinical consensus that in patients with

depression who have no prior history of bipolar disorder, a switch into mania or hypomania while they are on antidepressants may reflect an underlying bipolar diathesis. Although there is a continuing debate as to the best treatment strategy for such patients, many experienced clinicians and experts in the field treat these patients as suffering from a bipolar disorder, and the guidelines group concurs with such practice.

Clinical Recommendations

The quality of evidence and the working group classification of recommendation for each treatment modality are summarized in Table 1. The working group recommends that the mood stabilizer lithium should be the first choice in the treatment of bipolar depression (Figure 1) (71). In depressions with marked suicidality or severe psychosis, ECT should be considered earlier in the treatment algorithm. TCAs have the greatest predilection to induce a switch into mania and rapid cycling, so they should be avoided in the treatment of bipolar depression. If a patient with bipolar depression has been started on a TCA and appears to be responding well, the robust use of concomitant mood stabilizers such as lithium or divalproex is advisable.

Should treatment with an antidepressant become necessary to resolve depressive symptoms, SSRIs and bupropion are preferable because they may have a lower propensity to induce a mood switch. Bupropion is available in Canada directly from the manufacturers, although the sustained-release form is expected to be available shortly. There is no evidence that one class of antidepressants is better than another in terms of efficacy in the treatment of bipolar depression. It is inadvisable to use antidepressants without mood stabilizers in bipolar disorder. The consensus of the group was that the antidepressant medication should be gradually reduced and withdrawn completely within 6 to 12 weeks of remission of depressive symptoms. Despite the promising results with lamotrigine in the case series reported, further study of this compound is needed both in monotherapy and in combination with either divalproex or lithium.

Clinical Implications

- Bipolar depression can be treated effectively with medication.
- Switch into mania or hypomania is a common problem with antidepressant medication.
- Antidepressant medication should be withdrawn within 6 weeks of remission of depressive symptoms.

Limitations

- Many studies had a small number of subjects.
- Many antidepressant medications have not been tested in bipolar depressed patients.

Figure 1. Bipolar Depression.

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¹Assistant Professor and Director, Mood Disorders Clinical Research Unit, Department of Psychiatry, University of British Columbia, Vancouver, British Columbia.

²Associate Professor and Head, Division of Child and Adolescent Psychiatry; Director, Mood Disorders Group, Department of Psychiatry, Dalhousie University, Halifax, Nova Scotia.

³Assistant Professor, Department of Psychiatry, University of Toronto; Head, Bipolar Clinic, Clarke Institute of Psychiatry, Toronto, Ontario.

⁴Resident, Department of Psychiatry, Dalhousie University, Halifax, Nova Scotia.

⁵Associate Professor (Clinical) and Head, Outpatient Services and Mood Disorders Clinic, Department of Psychiatry, University of Sherbrooke, Sherbrooke, Quebec.

⁶Assistant Professor and Director, Mood Disorders Unit, Department of Psychiatry, University of Western Ontario, London, Ontario.

⁷Professor, Department of Psychiatry, University of Toronto; Head, Mood and Anxiety Disorders Division, Clarke Institute of Psychia-

try, Toronto, Ontario.

ADDRESS FOR CORRESPONDENCE: Dr LN Yatham, Department of Psychiatry, University of British Columbia, 2255 Wesbrook Mall, Vancouver, BC V6T 2A1
email: yatham@unixg.ubc.ca

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Section Five: Continuation and Prophylactic Treatment

Continuation and Prophylactic Treatment of Bipolar Disorder

Verinder Sharma, MD, FRCPC¹, Lakshmi N Yatham, MBBS, FRCPC, MRCPsych², David RS Haslam, MSc, MD³, Peter H Silverstone, MD, FRCPC, MRCPsych⁴, Sagar V Parikh, MD, FRCPC⁵, Raymond Matte, MD, FRCPC⁶, Stanley P Kutcher, MD, FRCPC⁷, Vivek Kusumakar, MBBS, FRCPC, MRCPsych⁸

OBJECTIVES: TO SUMMARIZE THE EVIDENCE FOR EFFICACY FROM PUBLISHED LITERATURE OF BIOLOGICAL TREATMENTS IN THE CONTINUATION AND MAINTENANCE PHASES OF BIPOLAR DISORDER, AS WELL AS THE RECOMMENDATIONS ABOUT DIFFERENT TREATMENT OPTIONS MADE BY THE WORKING GROUP WITHIN THE BIPOLAR SUB-COMMITTEE OF THE CANADIAN NETWORK FOR MOOD AND ANXIETY TREATMENTS (CANMAT).

METHODS: A REVIEW OF RELEVANT PUBLISHED LITERATURE AND PROCEEDINGS OF INTERNATIONAL CONFERENCES WAS CONDUCTED. THE QUALITY OF EVIDENCE WAS ASSESSED AND CLASSIFIED ACCORDING TO THE PERIODIC HEALTH EXAMINATION CRITERIA. TREATMENT RECOMMENDATIONS OF THE WORKING GROUP WERE BASED ON QUALITY OF EVIDENCE, A CONSENSUS OF EXPERT VIEWS, AND THE OPINIONS OF PSYCHIATRISTS AND FAMILY PHYSICIANS FROM ACROSS CANADA.

RESULTS: THERE IS OVERWHELMING EVIDENCE FOR THE EFFICACY OF LITHIUM IN THE PROPHYLAXIS OF BIPOLAR DISORDER. THE EVIDENCE FOR CARBAMAZEPINE IS LESS ROBUST. THERE ARE NO PUBLISHED DOUBLE-BLIND STUDIES WITH ADEQUATE NUMBERS OF SUBJECTS TREATED WITH DIVALPROEX SODIUM. *Since the publication of the Canadian Guidelines, the committee notes a study of prophylactic therapy with divalproex that is further examined in this chapter.*

CONCLUSIONS: DURING AND AT THE END OF THE CONTINUATION PHASE IT IS RECOMMENDED THAT MOOD STABILIZERS SHOULD REMAIN THE MAINSTAY OF THERAPY AND THAT OTHER TREATMENTS SHOULD BE GRADUALLY DISCONTINUED OR MAINTAINED ONLY IF

THERE IS VALID REASON TO DO SO. EFFICACIOUS MAINTENANCE TREATMENT CAN REDUCE MORBIDITY AND MORTALITY SIGNIFICANTLY AND IMPROVE PATIENTS' QUALITY OF LIFE.

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KEY WORDS: CONTINUATION, MAINTENANCE, PROPHYLAXIS, EXACERBATION, BIPOLAR DISORDER, LITHIUM, DIVALPROEX SODIUM, CARBAMAZEPINE, NEUROLEPTIC, ELECTROCONVULSIVE THERAPY

The continuation phase of the illness (also called the early stable phase) is defined as commencing once euthymia and resolution of psychosis have been achieved. The duration of this phase is usually between 6 and 12 weeks and is followed by a maintenance or prophylactic phase. Bipolar disorder is a chronic illness characterized by relapses (*reemergence of symptoms during continuation phase*), recurrences (*reemergence of symptoms in maintenance phase*), and remissions (*longer periods of relatively normal mood*).

Recurrence has been reported to be associated with substance dependence (1-5), the presence of psychotic features (1-3), and family history of schizoaffective disorder with manic features or mania (2,6,7). Duration of illness does not seem to correlate with the rate of recurrence (1,6). There is suspicion, however, based on schizophrenia research, that duration of illness before treatment is instituted may have a direct relationship with increased deficits and reduced treatment response. Available evidence suggests that electroconvulsive therapy (ECT) does not affect the rate of recurrence (8). Five-year and 4-year follow-up studies have failed to find the number of prior mood episodes to be a predictor of the number of subsequent episodes (1,6). Subsyndromal symptoms have been observed in 50% of patients in a 3-year treatment study, and these were associated with an approximately fourfold increase in risk of relapse or recurrence (9). Naturalistic study has also observed the rate of relapse or recurrence to correlate positively with the number of interepisode symptoms (10,11).

Predictive models have been used to study the cost (exposure to

lithium) versus benefit (prevention of relapse *or recurrence*) (12). The mortality of patients with untreated bipolar illness is 2 to 3 times higher than that of the general population; bipolar patients receiving treatment have a higher suicide risk when compared with the normal population (13). About one-quarter of bipolar patients attempt suicide (14).

To avoid psychopharmacotherapy that would induce unwanted side effects and be ineffective for target symptoms, clinicians must be able to determine which agent is most likely to be effective. Studies conducted to determine the predictors of response to treatment, however, have been mainly uncontrolled. In addition, in lithium studies the term “relapse” has been poorly defined (15), and the intraindividual treatment response is variable from one episode to the next (16). The predictive validity of applying predictors of lithium antimanic potential to prophylactic therapy is uncertain (17,18). Patients whose pattern of illness is mania followed by depression respond to lithium prophylaxis in approximately 80% of cases compared with a response rate of 25% to 30% in patients with a depression followed by mania and then a well interval pattern (15,19-21). Available data regarding prediction of prophylactic response to both divalproex and carbamazepine are weak and clinically not useful. Estimation of the risk of recurrence of mood episodes is less than precise.

Quality of Evidence and Recommendation

The quality of evidence is per the Periodic Health Examination format. The classification of recommendations from the working group is the product of expert opinions and a consensus process and reflects a global impression based on the quality of evidence for efficacy, adverse effects, tolerability, and acceptability of a given treatment for the patient.

Recommendation 17: Treatment During Continuation or Early Stable Phase

Treatment during Continuation or Early Stable Phase

The continuation phase begins with the return to euthymic mood and continues through the first six to twelve months of normal mood. Treatment recommendations for the continuation or early stable phase of acute mania are discussed below and illustrated in an algorithm (Figure 1). Psychoeducation continues, with or without the addition of concomitant psychotherapy, during this phase of illness recovery. The range of available psychosocial interventions

is discussed by Parikh and others in a previous article in this publication (22). Psychoeducation and psychotherapy are particularly important in fostering a collaborative approach in treatment with the patient. During this period, optimum serum levels of mood stabilizers *effective for the acute phase* are maintained, normal laboratory investigations are confirmed, and side effects are eliminated or minimized. The recommended approach to the use of mood-stabilizing agents during this phase will be discussed in the maintenance phase section of these guidelines.

The suggested adjustments to adjunctive medications during this phase of the illness are as follows:

BENZODIAZEPINES

A systematic evaluation of benzodiazepines as prophylactic agents in bipolar disorder has not been conducted. Chronic use of these agents is associated with tolerance, dependence, and withdrawal (23-26). Administration in the elderly increases the risk of potentially fatal accidents secondary to impaired coordination (27,28). The absence of prophylactic efficacy and attendant risks associated with long-term use support the gradual titration of these agents to either discontinuation or the minimal effective dose necessary for essential symptomatic management.

TYPICAL NEUROLEPTICS

In the absence of evidence to support continued use in maintenance therapy and in the presence of the possibility of sustaining serious side effects (29-34), gradual reduction and eventual discontinuation of these agents *late in* this phase of treatment is recommended unless there is a clear clinical indication to continue with the medication, for example, persistent psychotic symptoms. The lowest dose possible should be used for essential symptomatic

Figure 1. Continuation/Early Stable Phase.

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management. After a risk-benefit analysis, and if appropriate, attempts should be undertaken to discontinue these agents gradually. *For patients with severe problems with medication compliance, the clinician may wish to consider maintenance therapy with depot*

preparations of conventional antipsychotic medications.

ATYPICAL NEUROLEPTICS

Although risperidone and olanzapine may have better long-term side effect profiles, there are no currently available data for long-term efficacy of these agents in prophylaxis of bipolar mood disorder with the exception of a small case series for risperidone (35). An attempt should be made, therefore, to reduce and discontinue these agents within a few weeks of remission of acute symptoms. *There is one open randomized study, which involved a 52-week optimized treatment as usual in schizoaffective disorder and refractory bipolar disorder (Suppes, 1999). In this trial clozapine treatment was superior as prophylactic therapy on several outcome measures.* Clozapine is usually reserved for the treatment of severe refractory bipolar disorder patients, and hence it may need to be continued during the maintenance phase of treatment (36-38).

ANTIDEPRESSANTS

It is generally recommended that antidepressants be tapered and discontinued at the end of the continuation phase while mood stabilizer treatment is continued. The recommended duration of antidepressant administration during this phase cannot be derived from empirical evidence and is based on clinical judgement. *Generally, it is thought that continuation of antidepressant therapy should exceed what would have been the duration of an episode in the absence of treatment.* Where applicable, an estimation of this treatment interval can be based on the duration of previous depressive episodes. In the absence of such a history, a 6- to 12-week course is recommended when the patient is already on a mood stabilizer (39). Under the cover of a mood stabilizer, gradual downtitration over a 2- to 4-week period would be advisable in patients with antidepressant-induced mania, increased cycle acceleration, or precipitation of a mixed state (39). *At any point in the treatment, although mood may have improved, gradual reduction of the antidepressant dose may be appropriate if the patient is experiencing intolerable side effects, especially if compliance is threatened.*

ECT

ECT is a very effective treatment for acute mania. Maintenance ECT is sometimes used for patients who have had a high relapse rate.

The relapse rate after ECT administered during the acute phase and followed by lithium or antidepressant therapy is approximately 20% (40). Continuation ECT is indicated for patients who respond poorly to continuation medications or prefer ECT. During the continuation phase of the illness, ECT is usually indicated once weekly and the interval gradually decreased to once a month. Incomplete responders and those with a recurrent course may warrant more frequent ECT than at a monthly interval (40).

Summary of Continuation Phase Treatment

Acute-phase treatment can usually last from 2 to 10 weeks (*or for as long as the patient meets criteria for an acute mood episode*), and the end of the acute phase is defined as the point when the patient reverts to euthymia and the psychotic symptoms are resolved. The acute phase of treatment presents opportunities for psychoeducation of family and friends and for building a collaborative therapeutic relationship with the patient. *However*, the patient is often only able to tolerate and digest focal bits of psychoeducational information during the acute phase.

Significant psychoeducational and psychotherapeutic interventions commonly and appropriately occur in the continuation phase, which lasts for a further 6 to 12 weeks. Normalization of biological and social rhythms is also an essential part of management. Mood-stabilizing medication is the mainstay of pharmacotherapy. Neuroleptics and benzodiazepines, used for acute behavioural suppression or for rapid control of manic behavioural dyscontrol, need to be gradually discontinued over 2 to 3 weeks after symptom control has been achieved. Neuroleptics need to be continued well beyond the acute phase only if there are persistent or incongruent psychotic symptoms (*any psychotic symptoms*). Similarly, antidepressants can be gradually discontinued over 6 to 12 weeks after the remission from bipolar depression provided that the patient continues to be on a mood stabilizer. If there is a previous history of the patient's symptoms being exacerbated every time neuroleptics, antidepressants, or other psychotropic medications are discontinued, however, there is justification in continuing these medications in addition to stabilizers during this phase and beyond. The clinician and patient should constantly weigh the benefits versus risks of continuing or discontinuing treatments. This is also the phase for active discussion with the patient and family about long-term treatment and the benefits and risks of prophylactic treatment.

Serum medication levels and monitoring of bodily systems should be done as clinically indicated in the continuation phase.

Recommendation 18: Treatment During Maintenance or Prophylactic Phase

Treatment during Maintenance or Prophylactic Phase (Late Stabilization Phase)

Estimation of the risk of recurrence of mood episodes is less than precise. Early studies with lithium (17) and more recent unpublished studies with divalproex and lithium (Bowden and others 1996, papers at the American and Canadian Psychiatric Association meetings), *now published, Bowden et al., 2000*) suggest that these mood stabilizers may yield prophylactic benefit in moderate to severe illness, but there is a subgroup of patients, some with mild illness, who may not benefit from prophylactic treatment. There is no consensus, however, about how to identify this subgroup accurately or make reliable predictions, *so prophylaxis with a mood stabilizer is generally recommended for all subgroups with bipolar I disorder.*

Definitive indications for the commencement of long-term maintenance treatment with mood stabilizers and the duration of this therapy are not available. The decision to proceed with indefinite maintenance pharmacotherapy after a single manic episode has been supported by decision analysis, which analyzed the costs (that is, lithium exposure) and the benefits (that is, preventing relapse). Long-term lithium treatment has also been associated with a significant reduction in the mortality rate in patients with bipolar disorder (41).

The authors of these guidelines suggest that the continuation phase psychoeducation, biosocial rhythm normalization, and pharmacotherapies be continued *beyond the continuation phase* for not less than 6 months (preferably for 12 months) in those with a low risk and indefinitely in those with moderate to high risk of recurrence. Though empirical evidence has been inconsistent, variables proposed as presenting greater than a low risk of relapse in manic patients include poor occupational advancement prior to index episode (3), poorer psychosocial support (42,43), symptoms of depression (44), longer duration of illness (45), presentation of a mixed (46) or rapid-cycling state (47), comorbidity including history of alcoholism (1,3,48), psychotic features (1,6,49,50), and early (7) or late (45) age of onset. Moderate to high risk of recurrence is often dictated by the severity of illness and a strong family history of bipolar disorder. The assessment of moderate to high risk in a patient willing to accept maintenance treatment is an indication for psychoeducation, stabilization of biosocial rhythm, and prophylaxis pharmacotherapy of an indefinite duration. Treatment with benzo-

diazepines, neuroleptics, and antidepressants during the continuation or early stabilization phase has been discussed previously.

Long-term maintenance treatment with mood stabilizers is outlined below, and Table 1 presents the quality of evidence as per the Periodic Health Examination classification, as well as the recommendations for treatment made by the working group. The algorithm for treatment during this phase is shown in Figure 2.

LITHIUM

The prophylactic efficacy of lithium monotherapy has been demonstrated in controlled studies. Lithium maintenance therapy reduces both the frequency and severity of mood elevation and depression episodes in bipolar patients (51-59). Compared with placebo, the maintenance effect of lithium may reduce the recurrence of a major affective episode to 20% to 40% within 2 to 3 years of follow-up (51,52,54,60,61). The mean risk of recurrent major affective episodes of either polarity has been reported to be, on average, sixfold lower with lithium than with placebo (62). Non-compliance in uncontrolled clinical samples is probably associated with the higher rates of mood dysregulation or major episode relapse (63). The target range of lithium is to maintain a serum level of 0.8 to 1.1 mmol/L. The effects of a lithium serum level between 0.6 and 0.8 mmol/L are currently being studied, but there are no published data. At serum levels of between 0.4 and 0.6 mmol/L, the risk of relapse is increased by about 250% (62). The target serum lithium level would need to balance the risk of higher rates of relapse with the risk of side effects and thus noncompliance. Serum lithium levels in the lower range (0.4 to 0.6 mmol/L) carry a higher risk of relapse, but there is likely increased risk of noncompliance at the higher range (0.8 to 1.0 mmol/L) (58,64). Lithium dosing in the elderly requires that particular consideration be given to issues of tolerability due to changes in renal clearance.

Many patients will respond poorly to maintenance therapy with lithium (65). Inadequate efficacy includes partial remission, resolution of one but not the other phase of illness, and relapse following a euthymic period. A favourable lithium response is associated with a family history of bipolar illness and a previous mania-depression-euthymia sequence of illness (65,66). Factors that are somewhat predictive of a poorer response to lithium include rapid-cycling course and substance abuse (4) and a negative familial affective style (67,68). The quality of evidence for lithium maintenance therapy is "1," and the working group classified their recommendations as "A" (see Table 1).

DIVALPROEX SODIUM

The prophylactic efficacy of divalproex monotherapy in the prevention of bipolar episode relapse has been demonstrated in moderate to severe illness in a recent prospective, randomized placebo-controlled trial comprised of parallel placebo, lithium, and divalproex interventions over a one-year period (Bowden, unpublished observations). The fact that the follow-up in this trial was for a period of only one year and that the detailed results are unavailable, however, have prompted the committee to conclude that the efficacy of divalproex as a prophylactic agent in bipolar illness has not been proved at this stage, although many centres are using this agent for prophylaxis. At this time, the only published evidence comes from open studies (69-71). The quality of evidence, therefore, is "2.3," and the classification of recommendation, "B." *Since publication of the double blind placebo controlled trial by Bowden and colleagues, the committee has rated the quality of evidence a "1"; the classification of recommendation is "A".*

LAMOTRIGINE

Since the publication of these Canadian guidelines, additional information on the prophylactic efficacy of Lamotrigine has become available. This includes a large 18-month randomized, double-blind, placebo-controlled maintenance study of bipolar I patients (Calabrese JR, Bowden CL et al. 2001) and a 26-week double-blind, placebo-controlled maintenance study of rapid-cycling bipolar I and II patients (Calabrese JR, Suppes T et al. 2000). The 18-month study by Calabrese et al. revealed statistically significant evidence for the use of Lamotrigine in the prophylaxis of bipolar symptoms in bipolar I patients who were recently manic or hypomanic. The 26-week study showed Lamotrigine to be superior to placebo in rapid-cycling bipolar I and II patients. Lamotrigine was well tolerated in both studies. Based on these studies, the committee has rated the quality of evidence a "1"; the classification of recommendation is "B".

Table 1. Prophylaxis

Treatment	Quality of evidence ^a	Working group classification of recommendation ^b
Lithium	1	A
Divalproex	2.3 (1)	B (A)
Carbamazepine	1	C
Lamotrigine and gabapentin	na (<i>Lamotrigine 1</i>)	na (<i>Lamotrigine B</i>)
Lithium + divalproex	3	B
Lithium + carbamazepine	3	C
Divalproex + carbamazepine	3	C
Typical neuroleptic	1	D
Atypical neuroleptic	2.3	C
ECT maintenance therapy	2.3	C

^aQuality of evidence rating system:

- 1 At least one randomized controlled trial.
- 2.1 Well-designed controlled trial without randomization.
- 2.2 Well-designed cohort or case-controlled studies, preferably multicentre or from more than one research group.
- 2.3 Very significant results from uncontrolled trials from more than one centre comparing results with and without intervention.
- 3 Opinions of respected clinical authorities based on clinical experience, descriptive studies, or reports of expert committees.

^bClassification of recommendations:

- A Good support for the intervention to be considered in clinical practice.
- B Fair support for the intervention to be considered in clinical practice.
- C Poor support for the intervention to be considered in clinical practice.

- D Fair support for the intervention to be excluded from clinical practice.
- E Good support for the intervention to be excluded from clinical practice.

Figure 2. Maintenance/Prophylactic/Late Stable Phase.

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CARBAMAZEPINE

The prophylactic efficacy of carbamazepine has been demonstrated in both uncontrolled and double-blind cross-over comparisons with lithium and in double-blind, randomized placebo-controlled studies (72-74). Duration of follow-up, sample size, heterogeneity of the diagnosis, and confounding effects of concurrent medication all jeopardize the validity of its reported efficacy as a prophylactic agent in the treatment of bipolar disorder. Limited evidence of long-term prophylactic efficacy, including possible development of tolerance, poor patient acceptability, and rare, although serious, hematological side effects detract from the routine prophylactic use of this agent as an alternative to lithium (59,75-77). Maintenance use of carbamazepine as monotherapy or adjunctive therapy may be appropriate if initially proved to be effective in patients who recarbamazepine treatment in this phase is "1." The classification of recommendation made by the working group was "C" in view of limited evidence of long-term prophylactic efficacy, including possible development of tolerance, poor patient acceptability, and rare but serious hematological side effects.

ECT

Evidence of the prophylactic efficacy of long-term ECT has been contaminated by the concurrent administration of psychopharmacologic agents. Maintenance ECT may decrease the frequency and duration of major mood episode relapses. Possible indications for maintenance ECT include rapid relapse after ECT, relapse despite adequate maintenance medication, precipitous relapse of severe illness, inability to tolerate prophylactic medication, prior history of more favourable response to ECT as compared with maintenance medication, and patient preference in the setting of noncompliance with medication. Effective use of maintenance ECT

in case studies has been reported, but no controlled trials have been published (40,78). (Quality of evidence: “2.3”; classification of recommendation: “C.”)

TYPICAL NEUROLEPTICS

Minimal and methodologically limited evidence exists for the prophylactic efficacy of neuroleptics as mood stabilizers in bipolar disorder (29-32). Interpretation of these results is complicated by a small placebo-controlled crossover trial, with limited power to detect a difference, which reported depot neuroleptic administration to have no treatment value as a prophylactic agent in bipolar patients (33). Patients with mood disorders may be at a relatively high risk of developing tardive dyskinesia following treatment with these agents (34). The quality of evidence for typical neuroleptics is high (“1”), but the classification of recommendation was “D” because of concerns about long-term side effects such as tardive dyskinesia. *Depot neuroleptics are often used in clinical practice in patients who are unable to reliably adhere to a daily medication regimen.*

ATYPICAL NEUROLEPTICS

Uncontrolled trials and case studies report an effective role for clozapine in the continuation and maintenance phases of patients who had been refractory to therapy with conventional adjunctive agents (36-38). The prophylactic potential of risperidone in the treatment of bipolar disorder has also not been rigorously studied and remains uncertain. There is, however, a report of a small case series indicating the usefulness of risperidone in the maintenance treatment of bipolar disorder (35): quality of evidence, “2.3”; classification of recommendation, “C.”

MISCELLANEOUS TREATMENTS

A recent study with a small number of patients showed that those treated with a combination of lithium and divalproex (see Table 1) were significantly less likely to suffer a relapse or recurrence than patients treated with lithium and placebo (78). Although there are not adequate published data to guide clinicians about the value and efficacy of combining other mood stabilizers, experienced clinicians note that this can be a useful strategy, particularly in the refractory patient.

The prophylactic efficacy and associated risks of calcium channel blockers, thyroxine augmentation, and novel anticonvulsant agents (lamotrigine and gabapentin) remain unproved by rigorous

investigation (75,80-82). Insufficient evidence exists to support specific recommendations regarding the long-term use of these agents. If stability and euthymia are achieved with one of these agents in a refractory patient, however, it would be inadvisable to discontinue these medications for at least 1 to 2 years. In the absence of systematic and valid data, the working group could not make any recommendation for the use of these agents in the prophylaxis of bipolar disorder.

Recommendation 19: Special Populations

Special Populations

There is little in the way of published work at the extremes of the age range, but open studies with adolescents and the elderly suggest that mood stabilizers are an effective treatment (83,84) in acute mania. Although lithium can be effective in young people, there is some evidence that divalproex may be more effective in adolescent populations not only because mixed states and rapid cycling are more common in this age group but also because the side effects of lithium may be less acceptable to them (83). In the elderly, bipolar disorder is more commonly associated with medical and neurological difficulties. Although the anticonvulsants may be more acceptable to some of these patients, lithium may be as efficacious in this group (62). The specific issues of differential response by age or medical and neurological status have not been adequately studied. There is also no published work of well-designed studies of mood stabilizers in the prophylactic treatment of young people and the elderly.

The decision whether or not to use medications, particularly mood stabilizers, during pregnancy begins with a risk-benefit exercise in which the patient and her family should be fully involved (84). The risks of teratogenicity, which are present with all the mood stabilizers, although lithium likely poses a slightly lower risk, should be weighed against the risks of an illness recurrence, suicide, or the inability to look after self and the unborn child. If the patient's previous course of illness has been good with low severity and frequency of episodes, a planned pregnancy without mood stabilizers may be considered, with a gradual discontinuation of medication and a 4-week medication-free period before conception. Elective use of ECT, neuroleptics, and selective serotonin reuptake inhibitors in the first trimester can pose a lower relative risk to the fetus compared with mood stabilizers (85,86).

If a mood stabilizer must be used in the first trimester of pregnancy, clinicians should consider folic acid supplements with

anticonvulsants and also monitor for teratogenicity using appropriate investigations. Mood stabilizer dose may need to be raised as the blood and fluid volume increases during pregnancy to maintain a therapeutic serum level. If mood stabilizer is being continued during delivery, the doses need to be reduced drastically in order to avoid the toxicity caused by decreasing blood and fluid volumes immediately following childbirth.

The immediate postpartum period carries with it a greater than 50% risk of recurrence or exacerbation (87). Hence it is advisable to recommend reinstituting mood stabilizer treatment if this had been discontinued earlier, or ensuring that serum therapeutic levels are achieved and maintained. All mood stabilizers are secreted through breastmilk. There are pooled data to suggest that the medication or metabolites secreted through breastmilk do not pose a significant immediate risk to the newborn (86). Nevertheless, there are no long-term data available to rule out conclusively any behavioural effects on the developing child exposed to mood stabilizers during the newborn period. It is a common practice, therefore, to recommend discontinuing breastfeeding of the newborn if this is clinically appropriate.

Recommendation 20: Discontinuation of Pharmacotherapy

Discontinuation of Pharmacotherapy

The risk of recurrent bipolar episodes for those who discontinue lithium treatment has been reported in a metaanalysis to be as much as 28 times greater per month than for those who continue with lithium therapy (88). If lithium is to be discontinued for whatever reason, it should be withdrawn gradually over several weeks because studies suggest that the 5-year overall risk of recurrence in the rapid-discontinuation (< 2 weeks) group was 1.77 times higher (94.1%) than in the gradual-discontinuation group (53.3%). The 5-year rates of recurrence were 96% and 73% in bipolar type I and 91% and 33% in bipolar type II after rapid and gradual discontinuation, respectively (21).

The effects of abrupt discontinuation of anticonvulsants, antidepressants, benzodiazepines, and neuroleptics have not been systematically studied, although there is growing evidence in clinical practice that abrupt discontinuation provokes relapse. Whenever possible, gradual pharmacotherapy discontinuation over one month or more would be prudent.

Summary of Maintenance or Prophylactic Phase Treatment

If the patient has remained stable through the continuation phase of treatment, the clinician, patient, and family need to consider the value of prophylactic mood stabilizer treatment, which can reduce morbidity and mortality risks and improve the quality of life. The decision (see Figure 2) is relatively easier in patients who have had recurrent episodes, whose illness is very severe, or who have a strong family history of bipolar disorder. It is difficult, if not impossible, to predict accurately the minority of patients diagnosed with bipolar disorder who will never have a further mood disorder episode. Thus the recommendation for prophylactic treatment should be the rule. There should be very good reason not to recommend robust prophylactic treatment in a patient with a clear diagnosis of bipolar disorder. Apart from the rare patient who cannot tolerate any treatment, the decision to recommend indefinite prophylaxis may be deferred in patients with a single episode of hypomania with no history of depression and no family history of bipolar disorder. Even with these patients, however, every effort should be made to ensure mood stabilizer treatment for about a year. When medication is being discontinued, it should be done on a gradual basis over about 3 months, but not less than one month. Patients who discontinue treatment should have access to regular monitoring, rapid reassessment, and treatment if required.

Lithium is THE medication with proved prophylactic efficacy in bipolar disorder. It has been used in large numbers of patients, been tested in double-blind conditions, and been used over many years. It has demonstrated efficacy in classical, nonrapid-cycling, and nonmixed states, as well as in primary bipolar disorder, at serum levels of 0.8 to 1.1 mmol/L. There is growing evidence from several open studies that divalproex has significant prophylactic efficacy similar to lithium. At 2 recent conferences, the results of a double-blind multicentre study comparing lithium, divalproex, and placebo in the prophylaxis of bipolar disorder showed that divalproex and lithium had equal efficacy and were superior to placebo in patients with moderate to severe illness. This study is as yet unpublished. Divalproex may also be useful in early-onset bipolar disorder and in secondary bipolar disorder. There is some good evidence that carbamazepine has prophylactic efficacy, but more recently, its efficacy has come into question in long-term use and in rapid-cycling conditions. It too, like divalproex, is useful in secondary bipolar disorder.

Few patients manage a lifetime of bipolar disorder with monotherapy. Most require short- or long-term polytherapy with mood stabilizers and/or ECT. A very small subgroup of patients may be totally refractory to mood stabilizers and may require

maintenance ECT or an atypical neuroleptic like clozapine.

Serum levels of medication and other monitoring of bodily systems should be conducted as clinically indicated, but no less than once every 6 months.

Early Symptom Exacerbation

Subsyndromal mood dysregulation that does not satisfy major mood episode criteria is common in bipolar disorder. The differentiation between intermittent subsyndromal symptoms, which are the precursor of an impending acute episode, and a period of symptoms unrelated to a major mood episode can be difficult. Subsyndromal symptoms with depressive features have been described as often resolving without intervention (9,89). Those subsyndromal symptoms which are hypomanic in nature may have a greater risk of evolving into full affective episodes (9,89). Optimally, the patient and his or her significant others should be prepared in advance to recognize the precipitating factors and early manifestations of such episodes so as to facilitate prompt reassessment and appropriate intervention.

A recommended approach to the management of early symptom exacerbation is outlined in an algorithm (Figure 3). Should the patient tolerate an elevation of the existing mood stabilizer to the upper 20% of the therapeutic range, this may obviate additional pharmacologic augmentation. Insomnia may represent either a precipitant and/or an early symptom of mania. Nonresponders to the initial management strategies outlined in Figure 3 may require short-term pharmacologic augmentation or ECT (9,89). Such augmentation may include periodic use of a benzodiazepine to promote sleep with the intention of avoiding the precipitation of a major mood episode (90-92).

These guidelines have applied a classification previously used to standardize the definition of unipolar depression treatment phases (93). If symptoms meet the criteria for an acute episode following a period equal to or greater than 8 weeks of remission, it is considered to be a recurrence, whereas an acute episode within an 8-12 week period of the onset of remission would be considered a relapse. Progression to a major mood episode requires the initiation of treatment for the acute phase of illness.

Summary of Treatment of Symptom Exacerbation

It is not uncommon for patients who have been in remission to have exacerbations of symptoms. This may remain at a subthreshold level or, commonly, herald a full-blown episode of a mood

disorder. Patients, families, and support networks need education and training to recognize symptom exacerbations. Patients may not recognize symptom exacerbations and may depend on supportive family, friends, or clinicians to do so. Patients should have rapid access to reassessment. Identifying and managing psychosocial precipitants or stressors, ensuring adequate sleep, dealing with alcohol and substance abuse, ensuring optimum serum levels of medication, and ruling out adverse drug interactions are important. Nonresponders to these measures may require the addition of other relevant biological and psychosocial interventions to produce a remission and to prevent the entry into another acute illness phase.

Figure 3. Early Symptom Exacerbation.

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Clinical Implications

- Prophylactic treatment of bipolar disorder with mood stabilizers can reduce morbidity and mortality.
- Prophylactic treatment can also improve quality of life.

Limitations

- The evidence to support the use of carbamazepine and divalproex sodium for prophylaxis of bipolar disorder is limited.

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¹Assistant Professor and Director, Mood Disorders Unit, Department of Psychiatry, University of Western Ontario, London, Ontario.

²Assistant Professor and Director, Mood Disorders Clinical Research Unit, Department of Psychiatry, University of British Columbia, Vancouver, British Columbia.

³Resident, Department of Psychiatry, Dalhousie University, Halifax, Nova Scotia.

⁴Associate Professor, Department of Psychiatry, University of Alberta, Edmonton, Alberta.

⁵Assistant Professor, Department of Psychiatry, University of Toronto; Head, Bipolar Clinic, Clarke Institute of Psychiatry, Toronto, Ontario.

⁶Associate Professor (Clinical) and Head, Outpatient Services and Mood Disorders Clinic, Department of Psychiatry, University of Sherbrooke, Sherbrooke, Quebec.

⁷Professor and Head, Department of Psychiatry, Dalhousie University, Halifax, Nova Scotia.

Section Six: Department of Mental Health/Medical Assistance Additional Recommendations

Recommendation 21: Violence Toward Self or Others.

Persons with disorders of mood may be at risk of harm to self or others. This risk requires initial and ongoing assessment and should generally include the views of family, friends, caregivers, etc., as well as the setting where the assessment is made. Appropriate precautions should be taken whenever there are concerns about the safety of the individual or others. (The Surgeon General has issued a report that identified suicide as a major public health issue and health care providers should be familiar with this document.) (Satcher, 1999).

Patients with mood disorders may be at greater risk for acts of suicide or violence toward others when compared to the general population. The lifetime rates of suicide among subjects in the Epidemiologic Catchment Area database with bipolar, unipolar, and any other DSM-III-defined Axis I disorder were 29.2%, 15.9%, and 4.2% respectively (Regier et al., 1990).

Risk factors commonly associated with suicide have been studied in the literature. Risk factors that may be uniquely associated with suicide in persons with bipolar disorder include co-occurring substance use disorder, previous suicide attempt, family history of suicide, and access to lethal weapons.

Risk factors should be considered within the context of variables that are known to provide support: social support, having children, religious beliefs, and a meaningful purpose in life.

If the evaluator believes the individual to be at risk for suicide or other forms of violence, the treater is obligated to act in a reasonable manner to ensure that the individual is in a safe treatment setting that matches the assessment of risk. Vigilance needs to continue after such an acute episode subsides (Angst, 1999; Appelbaum, 1994; Monahan, 1992; Mulvey, 1994; Satcher, 1999; Swann, 1999; Tardiff, 1996).

Recommendation 22: Co-occurring Substance Use Disorders.

Bipolar Disorder is the Axis I disorder with the greatest lifetime prevalence of a co-occurring substance use disorder. The use of substances may represent a maladaptive form of self-medication for psychiatric illness.

The recommended treatment approach for co-occurring substance use disorders is integrated or collaborative for both disorders. Each disorder receives specific and appropriately intensive

primary treatment, which takes into account the complications resulting from the co-occurring disorders.

Recommended treatments for co-occurring substance use disorders should be individualized, and matched according to the specific diagnosis of each disorder, phase of treatment, and recovery, and for the acuity, severity, disability and motivations for treatment of each disorder at any point in time. Pharmacotherapy for co-occurring disorders should take into consideration the substance used and its impact on the therapeutic efficacy and safety of the mood-stabilizing agent (e.g., alcohol use in a person taking lithium carbonate) (Regier, Famer, Rae, et al., 1990).

Useful medications, such as benzodiazepines, should be monitored carefully if prescribed, to minimize the potential for abuse or dependency.

Recommendation 23: Integrating Culture into Clinical Practice.

“The U.S. mental health system is not well equipped to meet the needs of racial and ethnic minority population.” (U.S. Department of Health and Human Services, 1999). The Surgeon General’s Report on Mental Health includes an overview of Cultural Diversity and Mental Health Services. It reported that a constellation of barriers deters ethnic and racial minority groups from seeking and receiving quality treatment. These barriers include stigma, mistrust, help seeking behaviour, cost, clinician bias, and cultural obstacles. The overview enumerates the new challenges that clinicians face in meeting the treatment, psychosocial intervention, and psychoeducation needs of our culturally diverse clients. These clients experience the same barriers when suffering from Bipolar Disorder as they would with any other diagnosis.

When the culture of clinicians is very different from that of their clients, it may pose an extra challenge for clinicians to perform at the same level of clinical confidence and competence, when working with these clients. Awareness, knowledge, and skills to interact, assess, and treat clients in a cross cultural setting are helpful elements of quality of care, as are understanding how values, beliefs, customs, languages, and communication style influence the perception and expression of mental distress, symptoms and diagnosis.

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APPENDICES

MOOD DISORDERS
DIAGNOSTIC CRITERIA from DSM-IV
(American Psychiatric Association, 1994)

Major Depressive Episode

- A. Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure.

Note: Do not include symptoms that are clearly due to a general medical condition, or mood incongruent delusions or hallucinations.

- (1) depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad or empty) or observation made by others (e.g., appears tearful). **Note:** In children and adolescents, can be irritable mood.
- (2) markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation made by others).
- (3) significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day. **Note:** In children, consider failure to make expected weight gains.
- (4) insomnia or hypersomnia nearly every day.
- (5) psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down).
- (6) fatigue or loss of energy nearly every day.
- (7) feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick).

- (8) diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others).
 - (9) recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.
- B. The symptoms do not meet criteria for a Mixed Episode (see p. 114).
 - C. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
 - D. The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition (e.g., hypothyroidism).
 - E. The symptoms are not better accounted for by Bereavement, i.e., after the loss of a loved one, the symptoms persist for longer than 2 months or are characterized by marked functional impairment, morbid preoccupation with worthlessness, suicidal ideation, psychotic symptoms, or psychomotor retardation.

Manic Episode

- A. A distinct period of abnormally and persistently elevated, expansive, or irritable mood, lasting at least 1 week (or any duration if hospitalization is necessary).
- B. During the period of mood disturbance, three (or more) of the following symptoms have persisted (four if the mood is only irritable) and have been present to a significant degree.
 - (1) inflated self-esteem or grandiosity.
 - (2) decreased need for sleep (e.g., feels rested after only 3 hours of sleep).
 - (3) more talkative than usual or pressure to keep talking.
 - (4) flight of ideas or subjective experience that thoughts are racing.

- (5) distractibility (i.e., attention too easily drawn to unimportant or irrelevant external stimuli).
- (6) increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation.
- (7) excessive involvement in pleasurable activities that have a high potential for painful consequences (e.g., engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments).

- C. The symptoms do not meet criteria for a Mixed Episode (see p. 114).
- D. The mood disturbance is sufficiently severe to cause marked impairment in occupational functioning or in usual social activities or relationships with others, or to necessitate hospitalization to prevent harm to self or others, or there are psychotic features.
- E. The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication, or other treatment) or a general medical condition (e.g., hyperthyroidism).

Note: Manic-like episodes that are clearly caused by somatic antidepressant treatment (e.g., medication, electroconvulsive therapy, light therapy) should not count toward a diagnosis of Bipolar I Disorder.

Mixed Episode

- A. The criteria are met both for a Manic Episode (see p.113) and for a Major Depressive Episode (see p. 112) (except for duration) nearly every day during at least a 1-week period.
- B. The mood disturbance is sufficiently severe to cause marked impairment in occupational functioning or in usual social activities or relationships with others, or to necessitate hospitalization to prevent harm to self or others, or there are psychotic features.
- C. The symptoms are not due to the direct physiological effects of a

substance (e.g., a drug of abuse, a medication, or other treatment) or a general medical condition (e.g., hyperthyroidism).

Note: Mixed-like episodes that are clearly caused by somatic antidepressant treatment (e.g., medication, electroconvulsive therapy, light therapy) should not count toward a diagnosis of Bipolar I Disorder.

Hypomanic Disorder

- A. A distinct period of persistently elevated, expansive, or irritable mood, lasting throughout at least 4 days, that is clearly different from the usual nondepressed mood.
- B. During the period of mood disturbance, three (or more) of the following symptoms have persisted (four if the mood is only irritable) and have been present to a significant degree.
 - (1) inflated self-esteem or grandiosity
 - (2) decreased need for sleep (e.g., feels rested after only 3 hours of sleep).
 - (3) more talkative than usual or pressure to keep talking.
 - (4) flight of ideas or subjective experience that thoughts are racing.
 - (5) distractibility (i.e., attention too easily drawn to unimportant or external stimuli).
 - (6) increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation.
 - (7) excessive involvement in pleasurable activities that have a high potential for painful consequences (e.g., the person engages in unrestrained buying sprees, sexual indiscretions, or foolish business investments).
- C. The episode is associated with an unequivocal change in functioning that is uncharacteristic of the person when not symptomatic.

- D. The disturbance in mood and the change in functioning are observable by others.
- E. The episode is not severe enough to cause marked impairment in social or occupational functioning, or to necessitate hospitalization, and there are no psychotic features.
- F. The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication, or other treatment) or a general medical condition (e.g., hyperthyroidism).

Note: Hypomanic-like episodes that are clearly caused by somatic antidepressant treatment (e.g., medication, electroconvulsive therapy, light therapy) should not count toward a diagnosis of Bipolar II Disorder.

Rapid-Cycling Specifier

Specify if

With Rapid Cycling (can be applied to Bipolar I Disorder or Bipolar II Disorder)

At least four episodes of a mood disturbance in the previous 12 months that meet criteria for a Major Depressive, Manic, Mixed, or Hypomanic Episode.

Note: Episodes are demarcated either by partial or full remission for at least 2 months or a switch to an episode of opposite polarity (e.g., Major Depressive Episode to Manic Episode).

296.89 Bipolar II Disorder (Recurrent Major Depressive Episodes With Hypomanic Episodes)

- A. Presence (or history) of one or more Major Depressive Episodes (see p. 112).
- B. Presence (or history) of at least one Hypomanic Episode (see p. 115).
- C. There has never been a Manic Episode (see p. 113) or a Mixed Episode (see p. 114).

- D. The mood symptoms in Criteria A and B are not better accounted for by Schizoaffective Disorder and are not superimposed on Schizophrenia, Schizophreniform Disorder, Delusional Disorder, or Psychotic Disorder Not Otherwise Specified.
- E. The symptoms cause clinically significant distress or impairment in social, occupational, Or other important areas of functioning.

Specify current or most recent episode

Hypomanic: if currently (or most recently) in a Hypomanic Episode (see p. 115).

Manic: if currently (or most recently) in a Major Depressive Episode (see p. 112).

301.13 Cyclothymic Disorder

- A. For at least 2 years, the presence of numerous periods with hypomanic symptoms (see p. 115) and numerous periods with depressive symptoms that do not meet criteria a Major Depressive Episode.
- Note:** In children and adolescents, the duration must be at least 1 year.
- B. During the above 2-year period (1 year in children and adolescents), the person has not been without the symptoms in Criterion A for more than 2 months at a time.
 - C. No Major Depressive Episode (p. 112), Manic Episode (p. 113), or Mixed Episode (see p. 114) has been present during the first 2 years of the disturbance.

Note: After the initial 2 years (1 year in children and adolescents) of Cyclothymic Disorder, there may be superimposed Manic or Mixed Episodes (in which case both Bipolar I Disorder and Cyclothymic Disorder may be diagnosed) or Major Depressive Episodes (in which case both Bipolar II Disorder and Cyclothymic Disorder may be diagnosed).

- D. The symptoms in Criterion A are not better accounted for by Schizoaffective Disorder and are not superimposed on Schizophrenia, Schizophreniform Disorder, Delusional Disorder, or Psychotic Disorder Not Otherwise Specified.

- E. The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition (e.g., hyperthyroidism).
- F. The symptoms cause clinically significant distress or impairment in social, occupational,
or other important areas of functioning.

Appendix II: Monthly Mood Chart

Name _____

MOOD

Rate with 2 marks each day to indicate best and worst

[illegible]

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Instructions for Mood Charting

Gary Sachs, M.D.

Purpose:

This chart is intended to provide you with a simple means of generating a graphic representation of your illness over the last month. Mood charting will allow you to systematically bring together important pieces of information such as mediation levels, mood state, and major life events and to see emerging patterns that otherwise might be difficult to discern.

Mood charting is a good way to record events chronologically and will help you to report your mood and symptoms to your clinician more efficiently. After a few months the mood chart can be a useful tool in looking to the future. Once you begin to chart your mood and become accustomed to the chart, you will find it very quick and simple to enter information each day.

General

Instructions: Please fill in your name and DOB on each mood chart page. Each page is meant to chart one month at a time. Begin on the appropriate day of the month and continue charting until the end of that month. For example, if you begin the study on May 15th, continue charting until the end of May and begin June on another page. However, if you begin your chart at the end of a month, for example, May 27th, write in those last days of the month in the blank spaces before the first of the month and continue charting until the end of the next month.

Treatments: For each day, record the total number of tablets of each medication that you took. Draw a line through the box to indicate if the medication was not taken that day. If you are taking a medication PRN or only as needed, indicate this next to the name of the medication and enter the dosage of the prescription. In the case of PRN medication, mark the amount of tablets taken that day in the appropriate blocks.

Major

Life Events: In this column note any significant event that happened on that day. Include any event that you feel contributed to your mood state on that day or may have precipitated a future episode. Include suicide attempts, hospitalization, and psychotic symptoms.

Menses: For women, indicate days on which you had your period by circling the dates.

Mood

Ratings: There are three categories of mood ratings: Depressed, Elevated, or WNL (within normal limits).

For each day, mark an “X” in the block that appropriately describes your mood as its best and worst for that day (you will therefore have possibly 2 marks for each day). If symptoms of both mood elevation and depression are present in any given day, indicate the severity of each. Also, indicate the presence of any Psychotic Symptoms (hallucinations, delusions) on any day by marking an “X” in that column.

Drug Level: If you are taking Lithium, Tegretol (Carbamazepine), or Depakote (Valproate) and have had a blood level done, mark the level on the day that your blood was drawn and use the chart to indicate the level. For Lithium, mark the level with an “L”, for Tegretol use a “T” and for Depakote use a “D”.

Weight: Record your weight and the day on which you weighed yourself. You should weigh yourself on the same day each month (e.g., the 5th of each month).

INTRODUCTION

The Treatment of Bipolar Disorder: Review of the Literature, Guidelines, and Options

The Canadian Network for Mood and Anxiety Treatments (CANMAT) consists of a group of clinicians and clinical researchers from across Canada. The Bipolar Sub-Committee, the Depression Sub-Committee, and the Anxiety Sub-Committee form the core of CANMAT. Each of these groups has formed working parties to promote the drawing up of treatment guidelines, to coordinate continuing health education, and to conduct multicentre research studies.

The bipolar treatment guidelines and options emanated from a working party within the Bipolar Sub-Committee of CANMAT. The working group recognized that much new research and clinical opinion was pouring into the field of bipolar disorder and that many clinicians would value a practical set of treatment options and guidelines to promote evidence-based practice. Beginning in 1994, there have been at least 3 excellent publications focusing on one or 2 of the following areas: review of literature, consensus surveys, or guidelines or treatment options in bipolar disorder. This series is unique in that it combines a thorough review of literature, a classification of the evidence, consensus opinions and recommendations of Canadian physicians, and treatment options in different phases and stages in the treatment of bipolar disorder.

The steps in formulating the treatment options and guidelines included review of the literature (over 500 peer-reviewed articles, proceedings, or articles in press were studied, and a substantial number of relevant material has been referenced in this series of articles) and assessment of the quality of evidence from published work and work in press using the Periodic Health Examination classification, which is outlined below.

Quality of Evidence

- 1 At least one randomized controlled trial
- 2.1 Well-designed controlled trial without randomization
- 2.2 Well-designed cohort or case-controlled studies, preferably multicentre or more than one research group
- 2.3 Very significant results from uncontrolled trials from more

- than one centre comparing results with and without intervention
- 3 Opinions of respected clinical authorities based on clinical experience, descriptive studies, or reports of expert committees

Periodic Health Examination guidelines state that the rating for classification of recommendation be determined based on the efficacy of intervention. This was modified by the working group to include not only efficacy but also tolerability, adverse effects, and acceptability in developing recommendations and algorithms for treatment of bipolar illness. The working group recognized that there is a paucity of evidence from rigorous studies or inconclusive evidence in many areas of treatment of bipolar disorder.

Classification of Recommendations

- A Good support for the intervention to be considered in clinical practice
- B Fair support for the intervention to be considered in clinical practice
- C Poor support for the intervention to be considered in clinical practice
- D Fair support for the intervention to be excluded from clinical practice
- E Good support for the intervention to be excluded from clinical practice

Distribution of the working group's consensus and treatment algorithms developed from the contribution of 206 psychiatrists and 91 family practitioners in clinical practice from across Canada.

One hundred and sixty-four psychiatrists in clinical practice and 47 family practitioners from across Canada made valuable comments on and criticisms of the working group's consensus recommendations and the treatment algorithms. This information was collated and is incorporated into the recommendations. Experts on bipolar disorder both in Canada and in the United States also reviewed and made valuable comments, and these were incorporated as well. Finally, this series of articles went through an independent peer-review process before being accepted for publication.

This series of articles is the result of the above process. This supplement should be seen as an aid to a clinician who has to take into account many complex variables in determining treatment choice and management strategies for any individual patient. The treatment options and guidelines are not meant to be used as a

cookbook, a holy grail, or an alternative to good clinical judgement.

Acknowledgements

These guidelines and treatment options on bipolar disorder would not have seen the light of day but for the interest and endeavours of Ms. Kaveri Gupta, Research Assistant, Ms. Joan Wilson, Administrative Secretary, Drs Ghadirian and Bowen, the many psychiatrists and family practitioners who gave their time to offer suggestions and criticism, and the families of the authors who devotedly accepted the absence of loved ones when they were busy working on this task. CANMAT also acknowledges the Ontario Ministry of Health, Eli Lilly Canada, and Abbott Laboratories for the educational grants that they provided to facilitate the work of the depression, anxiety, and bipolar disorder working groups. The working groups have had total control over the process and content of the work. Neither government nor industry has had any input into the preparation of any of these guidelines or treatment options. This work is dedicated to the hundreds of thousands of sufferers and survivors of bipolar disorder, to their families and friends who offer invaluable support and succour, and to professionals of all disciplines who work with these patients and families.

Vivek Kusumakar, MBBS, FRCPC, MRCPsych
ASSOCIATE PROFESSOR AND HEAD
DIVISION OF CHILD AND ADOLESCENT PSYCHIATRY
DIRECTOR, MOOD DISORDERS GROUP
DEPARTMENT OF PSYCHIATRY, DALHOUSIE UNIVERSITY
HALIFAX, NOVA SCOTIA

Lashmi N Yatham, MBBS, FRCPC, MRCPsych
ASSISTANT PROFESSOR AND DIRECTOR
MOOD DISORDERS CLINICAL RESEARCH UNIT
DEPARTMENT OF PSYCHIATRY, UNIVERSITY OF BRITISH
COLUMBIA
VANCOUVER, BRITISH COLUMBIA

Appendix IV: DSM IV Outline for Cultural Formulation

OUTLINE FOR CULTURAL FORMULATION DIAGNOSTIC AND STATISTICAL MANUAL OF MENTAL DISORDERS

(American Psychiatric Association, 1994)

The following outline for cultural formulation is meant to supplement the multi-axial diagnostic assessment and to address difficulties that may be encountered in applying DSM-IV criteria in a multicultural environment. The cultural formulation provides a systematic review of the individual's cultural background, the role of the cultural context in the expression and evaluation of symptoms and dysfunction, and the effect that cultural differences may have on the relationship between the individual and the clinician. As indicated in the introduction to the manual (see p. xxiv), it is important that the clinician take into account the individual's ethnic and cultural context in the evaluation of each of the DSM-IV axes. In addition, the cultural formulation suggested below provides an opportunity to describe systematically the individual's cultural and social reference group and ways in which the cultural context is relevant to clinical care. The clinician may provide a narrative summary for each of the following categories:

Cultural identity of the individual. Note the individual's ethnic or cultural reference groups. For immigrants and ethnic minorities, note separately the degree of involvement with both the culture of origin and the host culture (where applicable). Also note language abilities, use, and preference (including multilingualism).

Cultural explanations of the individual's illness. The following may be identified: the predominant idioms of distress through which symptoms or the need for social support are communicated (e.g., "nerves", possessing spirits, somatic complaints, inexplicable misfortune), the meaning and perceived severity of the individual's symptoms in relation to norms of the cultural reference group, any local illness category used by the individual's family and community to identify the condition (see "Glossary of Cultural-Bound Syndromes" below), the perceived causes or explanatory models that the individual and the reference group use to explain the illness, and current preferences for and past experiences with professional and popular sources of care.

Cultural factors related to psychosocial environment and levels of functioning. Note culturally relevant interpretations of social stressors, available social supports, and levels of functioning and disability. This would include stresses in the local social environment and the role of religion and kin networks in providing emotional, instrumental, and informational support.

Cultural elements of the relationship between the individual and the clinician. Indicate differences in culture and social status between the individual and the clinician and problems that these differences may cause in diagnosis and treatment (e.g., difficulty in communicating in the individual's first language, in eliciting symptoms or understanding their cultural significance, in negotiating an appropriate relationship or level of intimacy, in determining whether a behaviour is normative or pathological.)

Overall cultural assessment for diagnosis and care. The formulation concludes with a discussion of how cultural considerations specifically influence comprehensive diagnosis and care.

